STUDY OF SUBFOVEAL CHOROIDAL THICKNESS IN VARIOUS STAGES OF DIABETIC RETINOPATHY USING EDI –OCT

DISSERTATION SUBMITED FOR

MS (Branch III) Ophthalmology

THE TAMILNADU DR. M.G.R MEDICAL UNIVERSITY

CHENNAI

APRIL – 2016

CERTIFICATE

This is to certify that dissertation entitled "**STUDY OF SUBFOVEAL CHOROIDAL THICKNESS IN VARIOUS STAGES OF DIABETIC RETINOPATHY USING EDI –OCT "** is a bonafide done by **Dr.R.Ram Sudarshan .** under our guidance and supervision in the department of Retina, Aravind Eye Hospital and Post Graduate Instuite of Ophthalmology in Madurai during his residency period from July 2013to April2016.

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DECLARATION

I**,Dr.R.Ram sudarshan** solemnly declare the dissertation titled **STUDY OF SUBFOVEAL CHOROIDAL THICKNESS IN VARIOUS STAGES OF DIABETIC RETINOPATHY USING EDI –OCT "** has been prepared by me. I also declare that this bonafide work or a part of this work was not submitted by me or any other for any award, degree, diploma to any other university board either in India or aboard

This dissertation is submitted to the **Tamil Nadu Dr. M.G.R Medical University**, Chennai in Partial Fulfilment of the rules and regulation for the award **of M.S. Ophthalmology (BranchIII**) to be held in April 2016.

Place: Madurai **DR.R.RAM SUDARSHAN.**
Date:

ACKNOWLEDGEMENT

I would like to pay my respects to **Dr.G.Venkataswamy,** the founder of Aravind eye care system and the source of inspiration that continues to drive the work here.

I thank **Dr.KimRamasamy**, Chief medical officer and HOD, Department of Vitreoretinal services, Aravind Eye care system for his guidance and advice.

I also like to thank **Dr.Manish Tandon**, Senior consultant, Dept of Vitreoretinal services for his continuous guidance and support throughout this work.

I also extend my gratitude **to Dr.Namperumalsamy**, Chairman emeritus, **Dr.Natchiar, Dr.M.Srinivasan** and **Dr.R.D.Ravindran,** Chairman, Aravind eye care system.

I also thank **Dr.N.Venkatesh Prajna**, Chief, Department of Medical Education for his guidance throughout my residency.

I thank **Mr.Vijayakumar,** Statistician, **Mrs.Kumaragurubari,** Librarian and **Mr.Govindarajan**, Librarian for their help in my study.

I am deeply indebted to the both the staff at the Vitreoretinal services and the patients involved in making this study possible.

I also thank my family and friends for their consistent support.

CONTENT S

INTRODUCTION

Diabetic retinopathy is one of the leading cause of blindness across the globe. Clinical and experimental research has shown that choroid may have a role in the pathology of Diabetic retinopathy.

Choroid is an important vascular tissue that supplies blood to RPE and photoreceptors[1]. Many vascular studies like ICG[2] as well as histopathological studies[3] have shown increased tortuosity, focal vascular dilatation in diabetic retinopathy.

Until recently, the choroid's inaccessibility essentially buried beneath the retina has made it a little understood anatomical structure. Today, we're able to image deeper into the eye than ever before, allowing us the opportunity to evaluate choroidal thickness and morphology both for the benefit of patient treatment and for a better understanding of diabetic retinopathy and other retinal diseases[4]. The technology making this possible is enhanced depth choroidal imaging, a function of optical coherence tomography.

With the spectralis OCT imaging of choroid is now possible. Studies have been done in caucasian and oriental population to assess choroidal thickness in diabetic Retinopathy .Studies have proven significant correlation with severity of diabetic Retinopathy.

Our study focuses on the assessment of subfoveal choroidal thickness in various stages of DR.

DIABETES

DIABETES MELLITUS:

Diabetes mellitus is the most common endocrine disease in adulthood which results from diminished secretion of insulin by BETA cells of islet of Langerhans.

PREVALANCE:

High percentage of patients belong to the non-insulin-dependent diabetes mellitus (NIDDM) or type 2 diabetes. Type 1 DM accounts for 15%of the diabetic population. Prevalence of Diabetic retinopathy according Wisconsin Epidemiological Study of Diabetic Retinopathy (WESDR) was 50.1%[5] .The incidence was 54.2% in the diabetes control and complications trial (DCCT)[6] in IDDM .The incidence was 35-39% in United Kingdom Prospective Diabetes Study (UKPDS)[7] in NIDDM.

In two studies[8-9] from South Indian population, the prevalence rates of Diabetic retinopathy in Non Insulin Dependent Diabetes Mellitus patients were 34.1% and 37%. According to the WHO, India has 62 million diabetic subjects at present as per the World Health Organization (WHO) estimates. In the Andhra Pradesh Eye Disease Study (APEDS)[10], it was reported that the incidence of DR was 22.4%. The Chennai Urban Rural Epidemiology

Study (CURES)[11], reported the incidence of DR to be 18% in an urban diabetic population

TYPES:

Patients with DM can be divided into two groups:

- Type 1 :Insulin dependent
- Type 2 :Non insulin dependent

Effect of hyperglycemia:

- Diabetic neuropathy
- Diabetic nephropathy
- Diabetic retinopathy

Effect of hyperglycemia on ocular tissues:[10]

- Diabetic retinopathy
- Diabetic papillopathy
- Dry eye syndrome
- Keratopathy

DIABETIC RETINOPATHY

Risk Factors:

General:

1. Duration of diabetes[13]
2. Metabolic control

Systemic Factors:

1. Nephropathy
2. Systemic hypertension
3. Pregnancy
4. Hyperlipidemia
5. obesity
6. Anemia

Pathogenesis of Diabetic retinopathy:

The triggering factor for DR is hyperglycemia. Cells which are not capable of bringing down the transport of glucose inside the cell in presence of increased blood glucose levels like the endothelial cells of the retinal capillaries are selectively damaged in Diabetes.

Sorbitol Pathway:

Excess glucose

Aldose reductase

Sorbitol

Accumulation of water by sorbitol

Pericyte Loss, decreased Photoreceptor function, decreased retinal blood flow and vasodilatation.

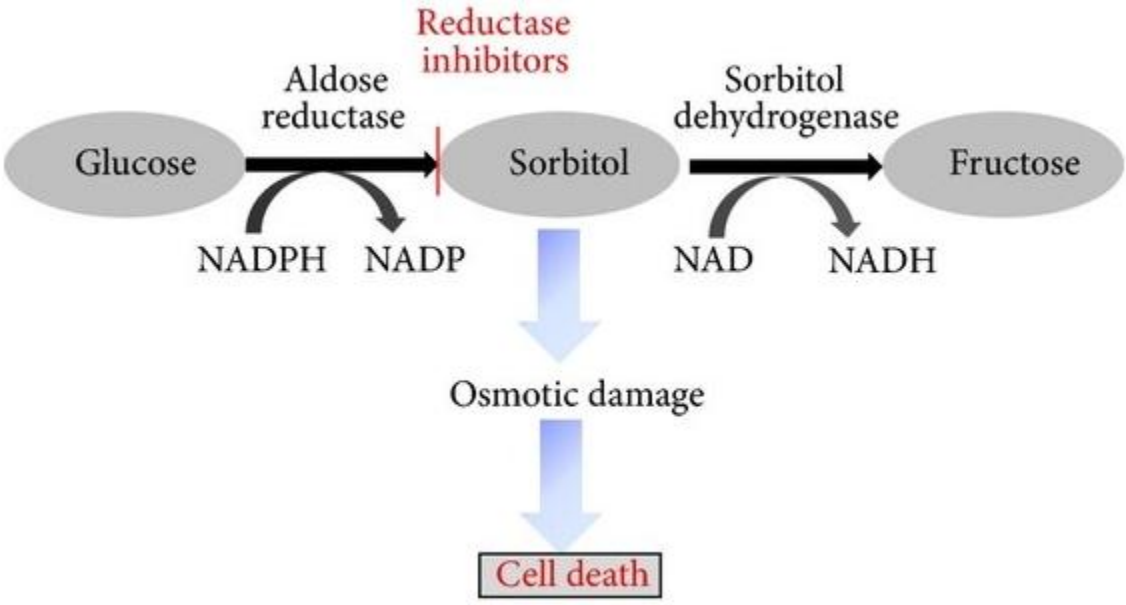


FIG 1. SORBITOL PATHWAY

Advanced glycation end products:

Adhesion of glucose with proteins

↓

Cross linking and AGE production

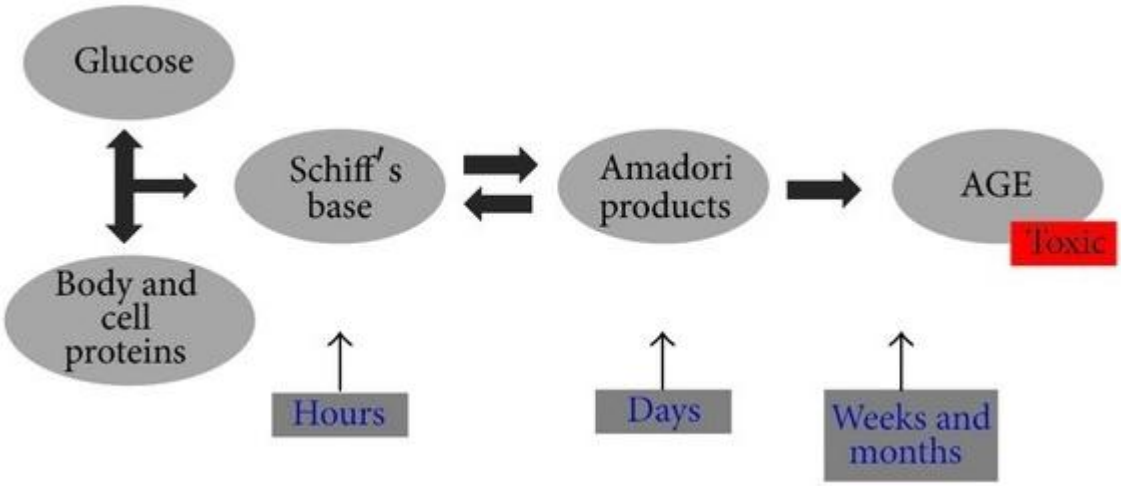


FIG 2. ADVANCED GLYCATION END PRODUCTS

Protein Kinase C pathway:

Incomplete glucose metabolism

↓

Accumulation of Diacylglycerol

↓

Increased activity of Protein kinase C

↓

Decreases retinal blood flow and blood retinal barrier breakdown

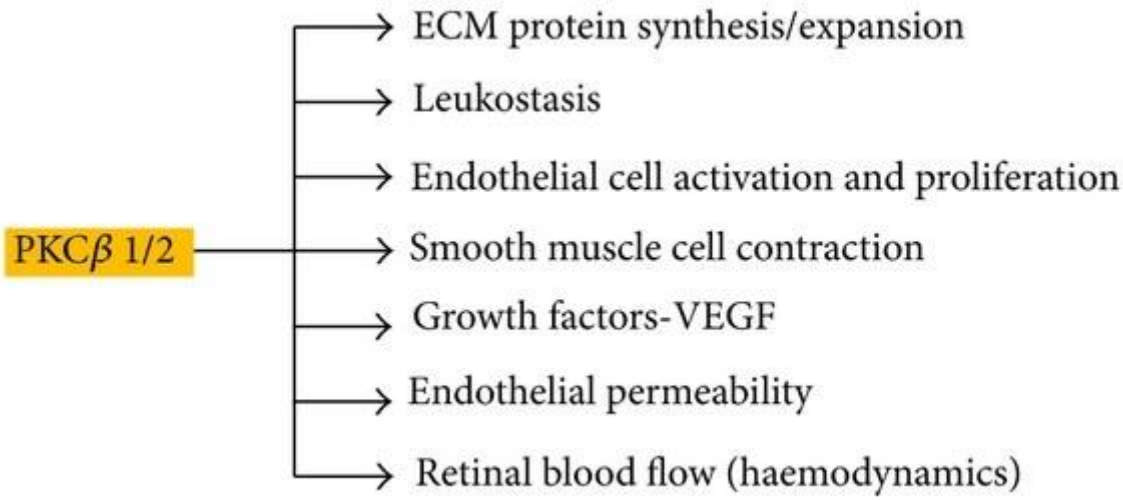


FIG 3. EFFECTS OF PKC

Free radicals:

Accumulated glucose and AGE products undergo auto oxidation resulting in free radical release. AGE inactivates anti-oxidant enzymes which remove excess free radicals.

Angiogenic factors:

Hypoxia

↓

Release of vasoendothelial growth factors by

RPE, Macrophages and T-cells

↓

Breakdown of Blood retinal barrier and neovascularisation in retina

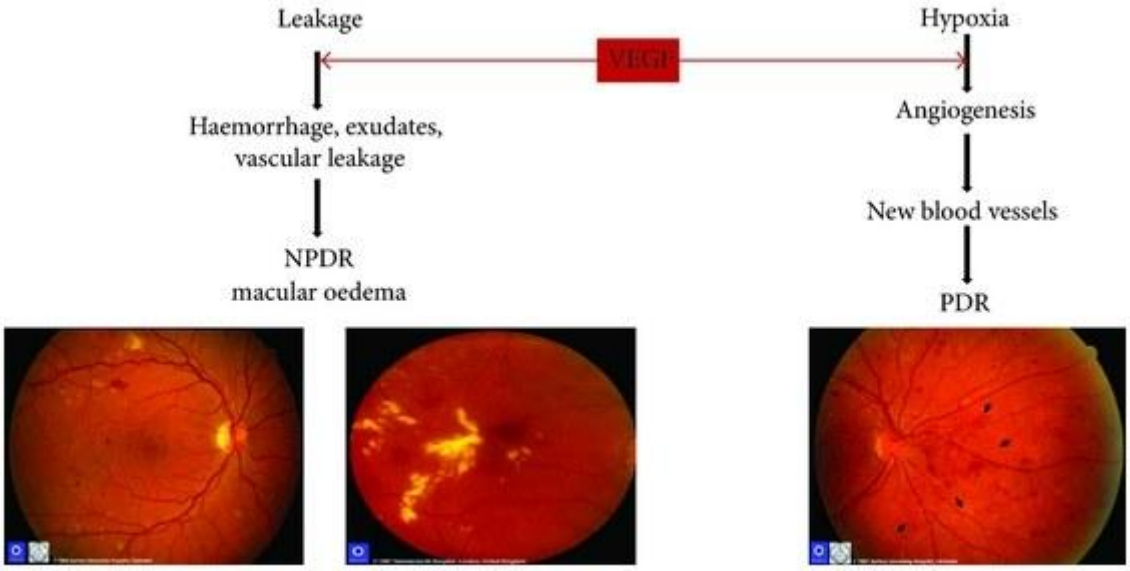


FIG 4. ANGIOGENIC FACTORS

Consequences of Diabetes in retina:

1. Microaneuryms –Leading to leakage
2. Retinal ooedema
3. Hypoxia:

It causes stimulation of:

1. Vasoendothelial growth factors which causes growth of new vessels.
2. Arterio-venous shunts – Intraretinal microvascular abnormalities.

Causes of vision loss in Diabetic retinopathy:

1. Macular ischemia
2. Macular oedema
3. Tractional Retinal detachment
4. Vitreous heammorhage
5. Neovascular glaucoma.

Classification of Diabetic retinopathy

It is classified on the basis of Early Treatment Diabetic Retinopathy Study.[14]

Early treatment Diabetic retinopathy study

Non –proliferative DR:

Very Mild:

Microaneurysms only

Mild:

Any or all of : microaneurysms, retinal haemorrhages, exudates, cotton wool spots, upto the level of moderate NPDR .No IRMA or significant beading.

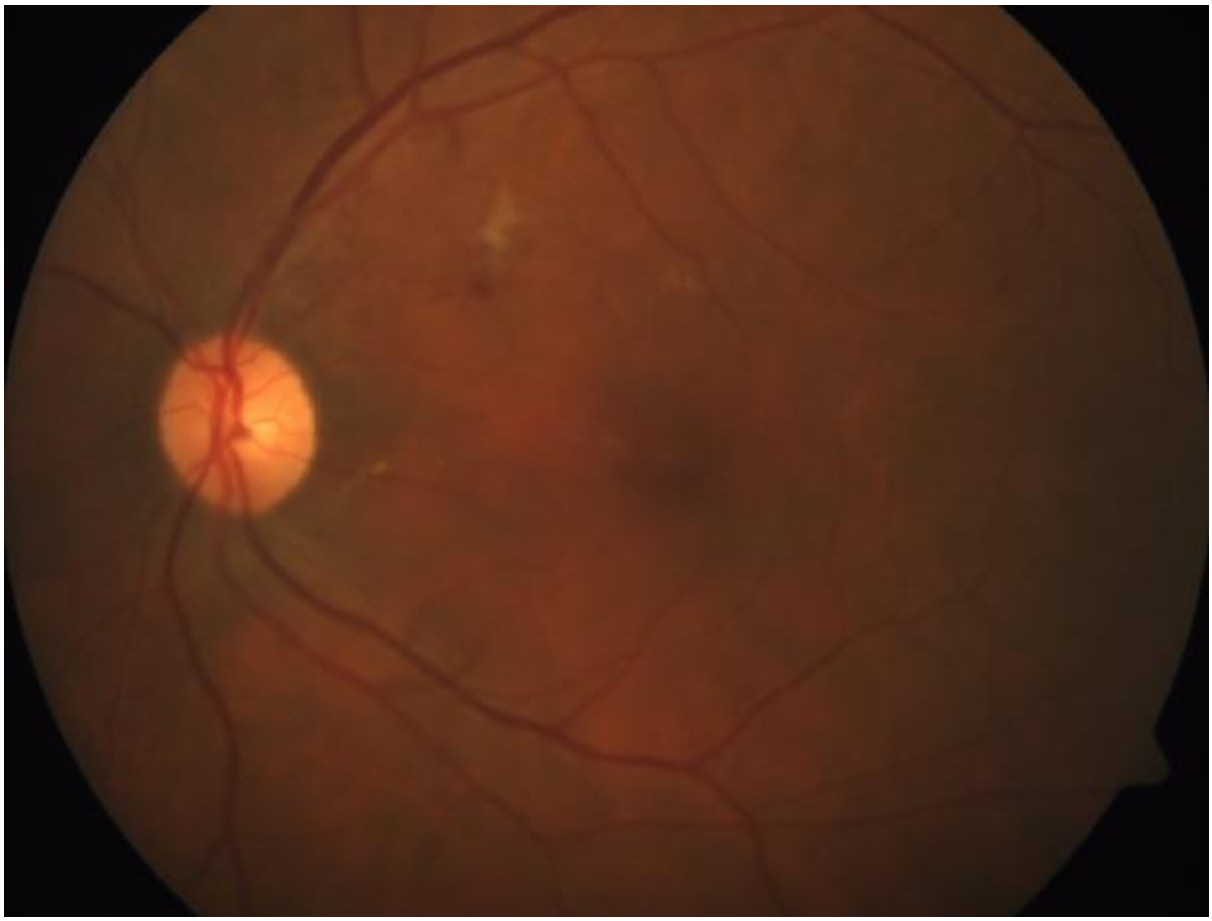


FIG 5.) MILD NPDR

Moderate NPDR:

Severe retinal haemorrhages (more than ETDRS standard photograph 2A:about 20 medium – large per quadrant) in 1-3 quadrants or mild intraretinal microvascular abnormalities.

Significant venous beading can be present in no more than 1 quadrant.

Cotton wool spots commonly present.

FIG 6 MODERATE NPDR

Severe NPDR:

4-2-1 rule: (One or more of following)

Severe haemorrhages in all 4 quadrants.

Significant venous beading in 2 or more quadrants.

Moderate IRMA in 1 or more quadrant.

FIG 7. SEVERE NPDR

Very Severe NPDR:

Two or more of the criteria for severe.

Proliferative Diabetic retinopathy:

Mild-Moderate:

New vessels on the disc NVD or new vessels elsewhere (NVE) ,but extent insufficient to meet high risk criteria.

High-Risk PDR:

New vessels on the disc (NVD) greater than ETDRS standard photograph 10 A(1/3 disc area).

Any NVD with vitreous or pre retinal haemorrhage.

NVE greater than ½ disc area with vitreous or pre retinal haemorrhage (or haemorrhage with presumed obscured NVD/NVE)

Advanced Diabetic Eye disease:

1. Persistent Vitreous haemorrhage
2. Neovascular Glaucoma.
3. Tractional Retinal detachment

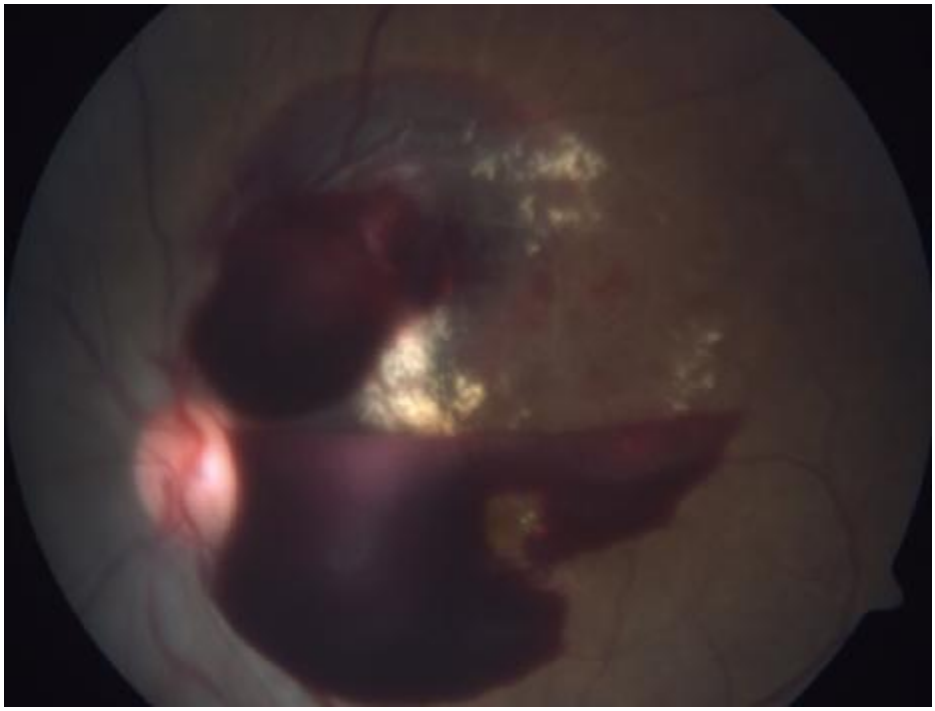


FIG 8. PDR

Diabetic Macular oedema:

It is the most common cause of visual impairment. The leaked fluid from the microaneurysms is initially collected between the outer plexiform and inner nuclear layers.Later it may involve the inner plexiform and nerve fibre layers.

Focal Maculopathy:

Caused by focal leakage from microaneurysms.Incomplete or complete ring of hard exudates may be present

Diffuse Maculopathy:

Due to generalized leakage from capillaries.

Ischemic maculopathy:

Characterised clinically by presence of reduced visual acuity in association with relatively normal appearance of macula although haemorrhage and exudates may be present elsewhere.

Clinically significant Macular oedema:

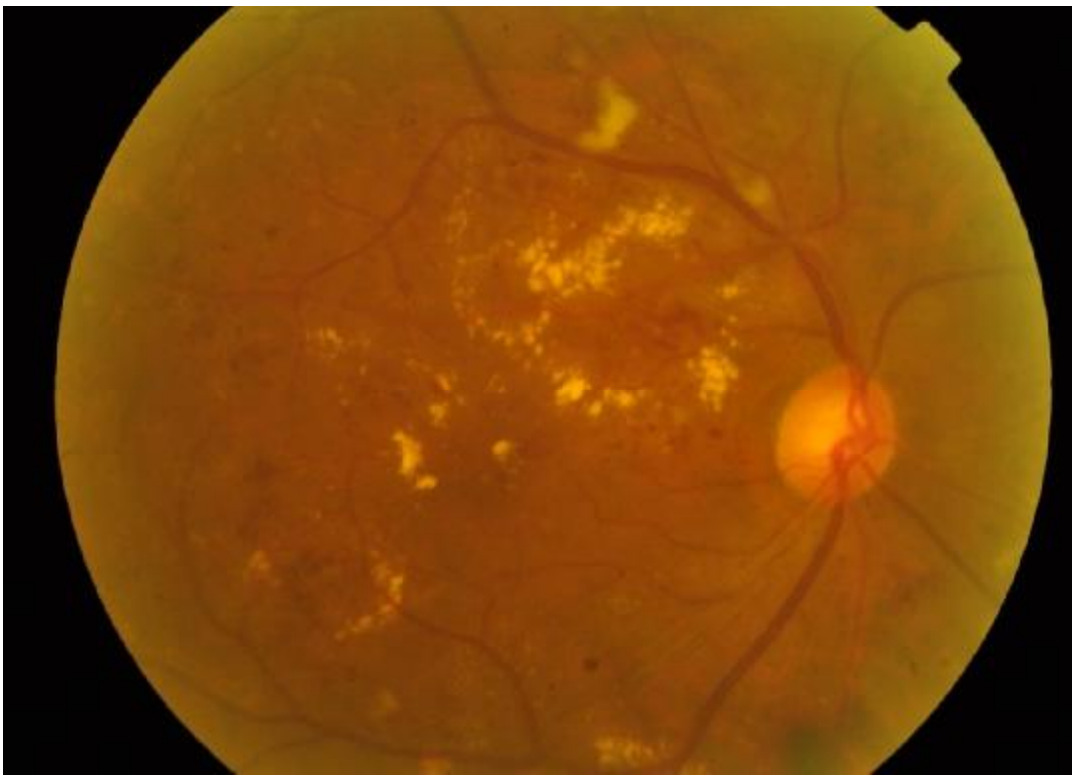


FIG 9 CSME

Was defined in ETDRS as:

" Hard exudates at or within 500 micrometers from the centre of the macula with adjacent retinal thickening

Retinal thickening at or within 500 micrometersfrom the centre of the macula.

Retinal thickening of 1500 micrometers or more, any part of which is within one disc diameter of the centre of macula".

CHOROID

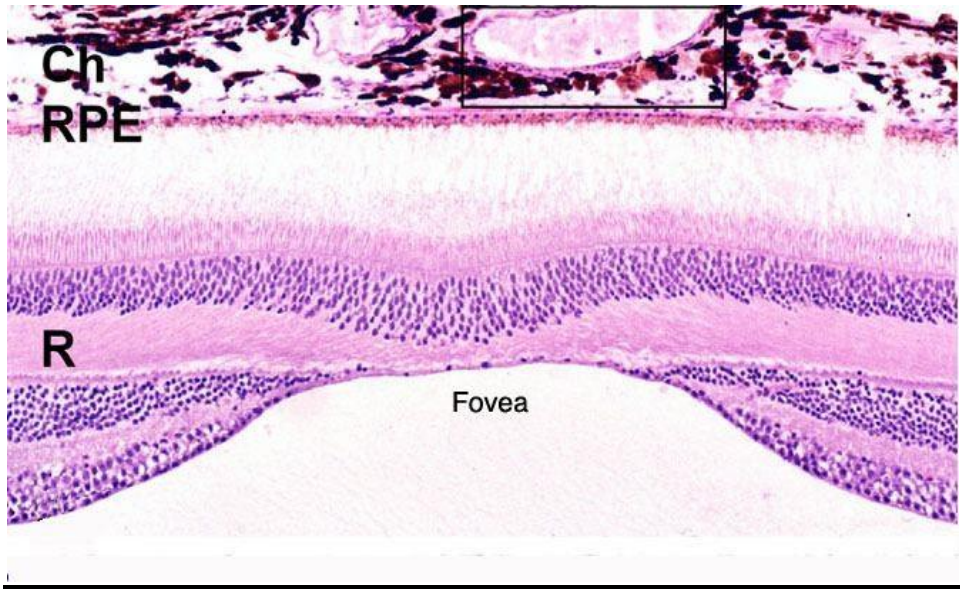


FIG 11. CH –CHOROID; RPE –RETINAL PIGMENT EPITHELIUM, R-RETINA

Development:

Choroid develops from the neural crest cells[15,16,17]. The choroidal stroma develops from the neural crest cells which condense and differentiate into it (Ensheated choroidal stroma).The embryonic annular vessels are formed by the mesenchymal tissue which is invaded early by the endothelium lined blood spaces. The choriocapillaris differentiate during the fourth week of gestation.

The fenestrations which are the characteristic feature of the choriocapillaris develop after the seventh week of gestation. This

development takes place alongside the thinning of endothelium, enlargement of the vessel lumen, increase in the number of intracellular vesicles. Basal lamina also becomes well defined, continuous and thicker.

The endothelium of the choriocapillaris is the last to be organised.

At the end of the second month certain stuctures can be distinguished better like:

1. Branches of short posterior ciliary arteries
2. Rudimentary vortex veins..

Timeline for development of layers of choroid:

First and second month: Capillaries

Third month: Haller layer and choriocapillaris (bruch's membrane derives from the choriocapillaris)

Fifth month: Sattler layer.

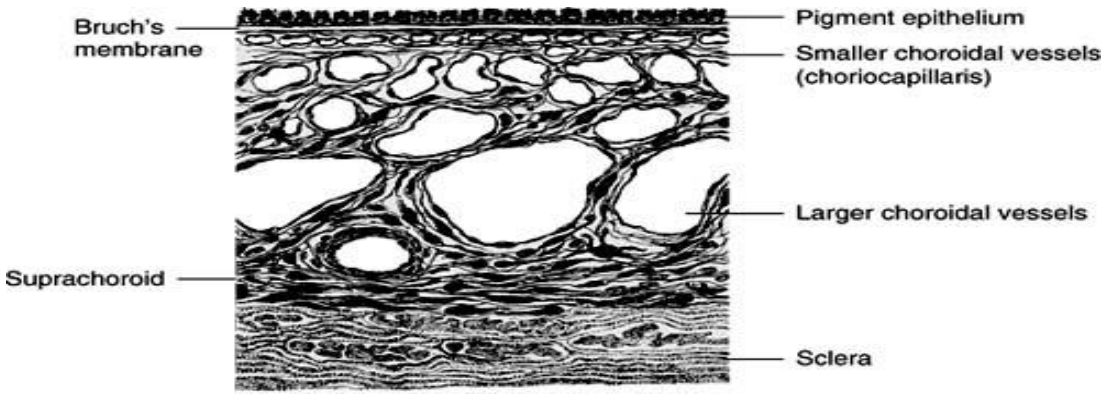


FIG 12. LAYERS OF CHOROID:

Anatomy:

Choroid is an soft, pigmented, extremely vascular tissue present between the retina and the sclera.

Anteriorly it extends from the optic nerve to the oraserrata. The smooth inner surface is firmly attached to the sclera in both the region of the optic nerve and also aroundthe area where the vortex veins exit the eyeball.

The long and short posterior ciliary arteries and present in the suprachoroidal lamina which is a pigmented sheet lying between the choroid and the sclera.

Layers of choroid:

It can be divided into

1. Bruch's membrane
2. Choriocapillaris
3. Sattler's layer
4. Haller's layer

Bruch's Membrane:

The bruch's membrane is a thin noncellular multi-layered structure extending fromoraserrata to the optic disc. It lies between the choriocapillaris and the RPE. It consists of five layers:

1. The inner basal lamina lies is in continuity with the basal lamina of ciliary epithelium. Retinal pigment epithelium is separated by a 100 micrometre wide zone.
2. Interweaving collagen fibres forms the inner collagenous zone .It is 1 micrometers in thickness
3. Elastic zone is composed of dense cortex and a homogenous core of interwoven band of elastic fibres.
4. The outer collagenous zone is structurally similar to the inner zone.
5. A non-continious sheet across bruch's membrane is formed by the Basement membrane of choriocapillaris.

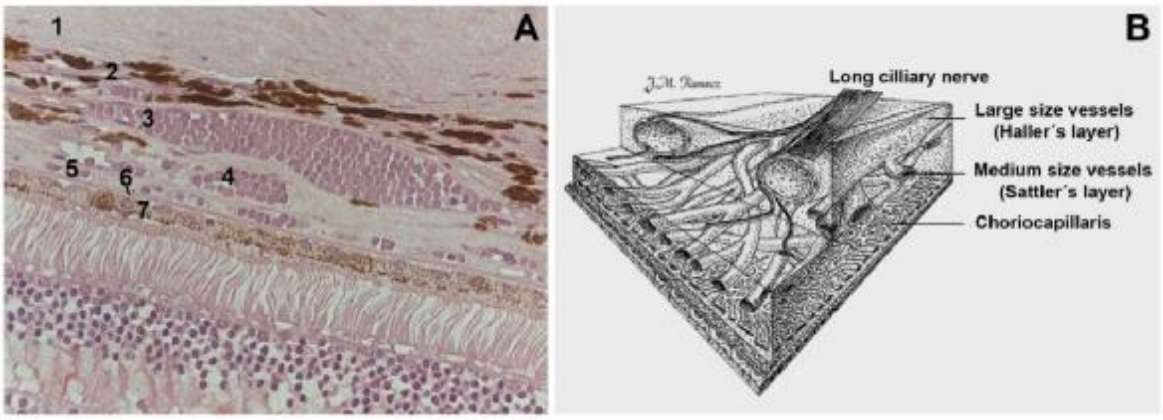


Fig13) Layers of choroidal vasculature A: Histological section (H/E). B: Three-dimensional scheme 1: Sclera; 2: Suprachoroid; 3: Haller´s Layer; 4: Medium-sized vessel layer Sattler´s Layer; 5: Choriocapillaries; 6: Bruch´s membrane; 7: Retinal pigment epithelium

Choriocapillaris:

The choriocapillaris is formed by a lobular organization of wide lumen capillaries.It supplies an independent segment of choriocapillaris. It lies in a single plane.

The lobular network is well developed at the posterior pole. It is less regular at the ora serrata anteriorly.

8 – 16 precapillary arterioles feeds the submacular choroid where marked interateriolar anastomosis is present.

Studies have shown that the lobular anatomy is venocentric. Here, the draining venules are present more centrally whereas the feeding arterioles are situated at the periphery. Occlusive events in the choroid and at the optic nerve are due to the presence of vascular watershed zones which are created by the lobules which are arranged in a mosaic pattern with very little anastomosis between them.

The vessel walls are extremely thin and contain multiple fenestrations, especially on the surface facing the retina .They show junctions of the zonula adherens type, so zonula occludens is not well developed as in the retinal capillaries. Pericytes are located along the outer wall. As a result, small molecules such as fluorescein, which diffuse across

the endothelium of the choriocapillaris, do not leak through medium and large choroidal vessels.

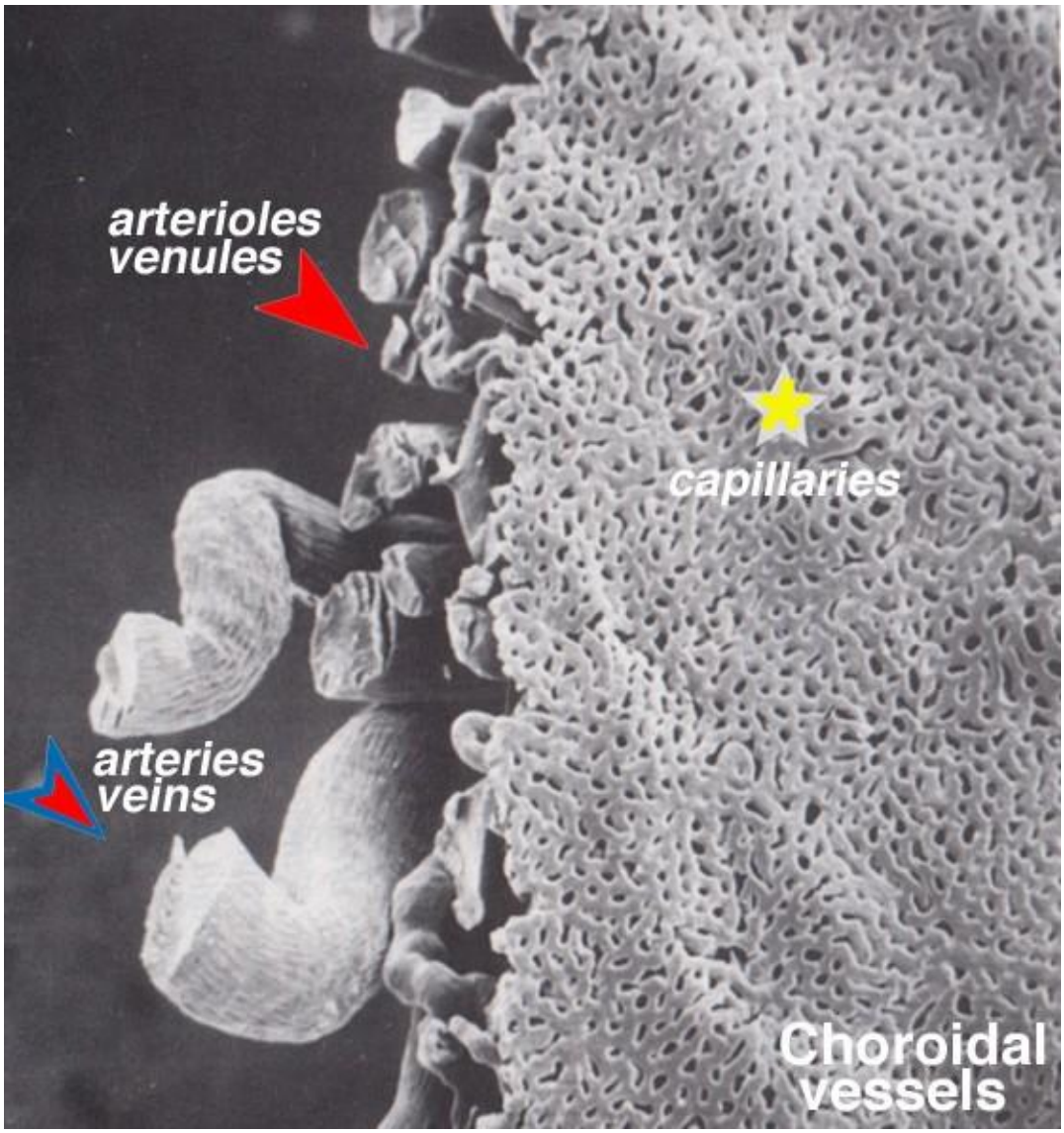


FIG 14 : SHOWING LAYERS OF CHOROID: OUTER ARTERIES AND VEINS (RED /BLUE ARROW), MEDIAL ARTERIOLE AND VEIN (RED ARROW), INNER CAPILLARY BED (STAR)

Haller's and Sattler's layer:

The middle and outer choroidal vessels are not fenestrated. The large vessels typical of small arteries elsewhere, possess an internal elastic lamina and smooth muscle cells in the media. As a result, small molecules such as fluorescein, which diffuse across the endothelium of the choriocapillaris, do not leak through medium and large choroidal vessels.

Abundant melanocytes as well as occasional macrophages, lymphocytes, mast cells, and plasma cells appear throughout the choroidal stroma. The intercellular space contains collagen fibers and nerve fibers. The degree of pigmentation observed ophthalmoscopically in the ocular fundus primarily depends on the number of pigmented melanocytes in the choroid. Melanosomes are absent from the RPE and choroid of albinos.

The degree of pigmentation in the choroid must be considered when one is performing photocoagulation, because it influences the absorption of laser energy.

Thickness of Choroid:

The thickness of choroid was found to be 100 -200 micrometres. The thickness was greatest belowthe macula (500 -1000 micrometres).

Spaide et al[4] noted that choroid was thickest in the subfoveal region and was reported thinner nasally than temporally.

Blood Supply:

The long and short posterior ciliary arteries along with the perforating anterior ciliary arteries supply the choroid. Venous drainage is through the vortex system. The blood flow in choroid is higher than other tissues in the human body.

As a result, the oxygen content of choroidal venous blood is only 2%-3% less than that of arterial blood.

The close proximity of the choroidal watershed zones to the peripapillary region and the macula may prove the possible role of choroidal blood flow in ischemic optic neuropathies and in macular ischemic lesions.

Choroidal watershed zones:

The border between the areas of distribution of any two end- arteries in a tissue is called a 'water-shed' zone. All choroidal arteries are end arteries. The choroidal vasculature has several such watershed zones, which are arranged as follows:

- Between Posterior ciliary arteries (PCA)
- Between short PCA

- Between the short and long PCAs
- Between the PCAs and the anterior ciliary arteries
- Between the choriocapillaris lobules
- Between the vortex veins

The close proximity of the choroidal watershed zones to the peripapillary region and the macula may prove the possible role of choroidal blood flow in ischemic optic neuropathies and in macular ischemic lesions.

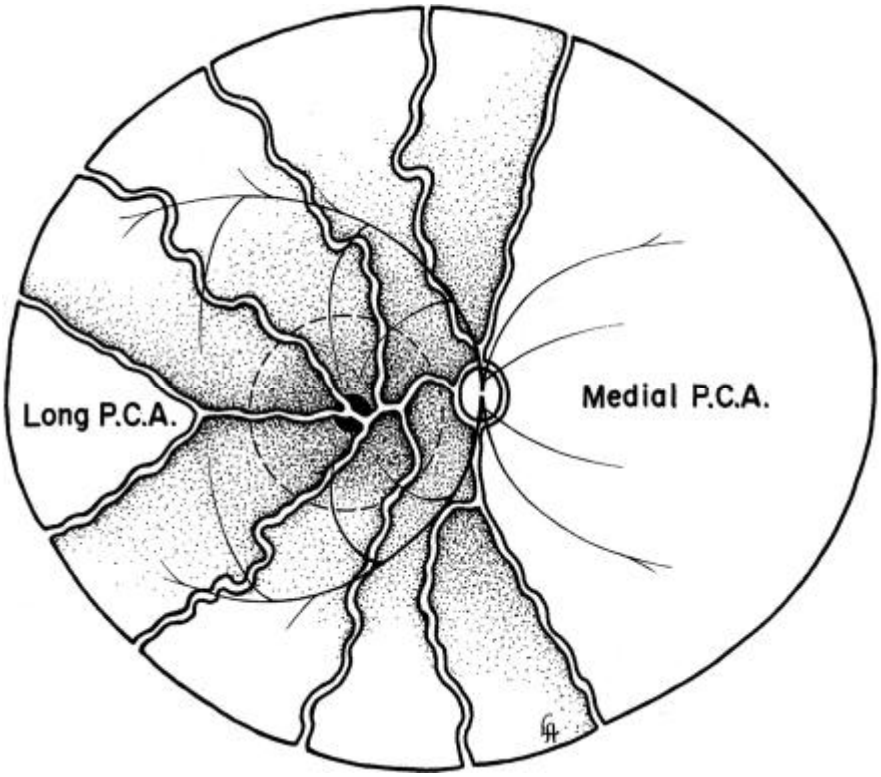


FIG 15. WATERSHED ZONES

Functions of choroid:[18]

1. Supplying oxygen and nutrients to RPE and photoreceptors
2. Thermoregulation via heat dissipation

3. Light absorption
4. Controls IOP through the vasomotor control of blood flow
5. Drainage of aqueous humor through the uveoscleral pathway.

Autoregulation:

It is a process within many biological systems wherein an internal mechanism which is adaptive in nature works to mitigate or adjust the biological systems response to stimuli. It is most commonly present in the kidney, heart and brain and most systems of the body have some amount of autoregulation.

In human choroids, varying degrees of autoregulation have been found. Decrease in perfusion pressure may be induced by changes in blood flow which is elicited by step increases in intraocular pressure (IOP)[19].Isometric exercise also brings about an increase in the perfusion pressure[20].But these changes in blood flow were not linearly related to the changes in perfusion pressure, indicating presence of some degree of autoregulation. Studies[21] have noted that there was an increase in choroidal blood flow by approximately 1.5% /mm Hg PCO2 when there was increase in the levels of arterial CO2 tension.

DIABETIC CHOROIDOPATHY

The main characteristic finding in diabetic microangiopathy is the thickening of basement membrane in capillaries of all organs including choroid [22-26]. In addition to these changes the other findings in the choroid are:

Histopathalogical changes:

Hidyat et al[3] in his study noted that there was presence of:

1. Obstruction of choriocapillaris
2. Choroidal aneurysms
3. Choroidal neovascularisation
4. Loss of viable endothelial cells
5. Degeneration of choriocapillaris.

Indocyanine green Angiography:

Weinberger et al[2] in his study found that there was presence of

1.) Hypoflourescent spots:

a. Due to ischemic changes of choroid
b. Defect of choriocapillaris

2.)Hyperflourescent spots:

a. Due to choroidal neovascularisation leading to leakage.

b. Due to presence of intra –choroidal microvascular abnormalities.

Laser Doppler flowmetrey:

Nagoka et al[27]reduction in blood volume in sub foveal area in non proliferative diabetic retinopathy and more markedly in Proliferative diabetic retinopathy.

FACTORS AFFECTING CHOROIDAL THICKNESS

Within choroid:

Tonicity of Choroid:

Changing the tonicity of the choroid is one of the likely mechanisms by which choroidal expansion can take place. Wallman et al[28]has shown that the eyes which are recovering from deprivation-induced myopia synthesize markedly higher amounts of proteoglycans than choroids from normal eyes leading to rapid increase in choroidal thickening.

Movement of fluid from RPE:

In studies[29], it was found that movement of ions and fluids from the RPE and outer retina into the choroid via the RPE pump could cause an increase in choroidal thickness if the movement of solutes from the choriocapillaris from the choroid into retina do not match the same.

Changes in Vascular permeability:

Increase in capillary permeability results in an increased movement of fluid from choroidal vessels which in turn has an effect on the choroidal thickness .This movement causes the proteins to move into extracellular matrix and followed by passive fluid flow [30-32].

They also found that protein content in suprachoroidal fluid is decreased in thinned choroids (deprivation myopia) and is more in thicker choroids. The reason being in all deprivation induced myopia the protein content was more , thus making the choroid thinner and the protein content was less in recovering eyes making the choroid thicker.

Movement of fluid from Anterior chamber to choroid:

Another factor which can affect the choroidal thickness is movement of aqueous from the anterior chamber through the ciliary muscleinto the choroid. This movement of aqueous into the choroid increases the size of the lacunae thereby affecting its thickness.

Wallman et al[28] found that choroidal lacunae and anterior chamber were connected by injection of horseradish peroxidase into the anterior chamber. Tracer molecules were found four hours later in the lacunae of suprachoroid.Pendark et al [33] also found presence of fluorescein Dextran in suprachoroidal space after injecting it into anterior chamber.

Systemic:

Diabetes:

Histological examinations have proved that there is presence of increased tortuosity of the blood vessels, focal vascular dilatation ,

narrowing of vessels with hypercellularity and vascular loops and microaneurysm formation.[3]

In previous studies investigations have reported selective filling of choriocapillaris in indocyanine angiography[2] and a reduction of blood flow in Doppler studies[27].The decrease in blood flow was postulated to be secondary to retinal hypoxia.

Adhi et al[34] showed that due to closure of choriocappillaris in diabetic eyes there is an reduction in the choroidal vessel layer as well as the thickness of the choriocapillaris. Regatieri et al[35] proposed that since the choroid was the major source of nutrition for the RPE, the reduction in choroidal thickness was due to the hypoxia of retinal tissue.

Hypercholestremia:

Salazar et al[36] has shown that hypercholestremia produces atherosclerotic changes of the choroid which leads to increase in thickness in animal models. He also stated that there is no reversal of the thickening once there is normalisation of cholesterol levels.

Salazar et al[36] also proved that there is hypertrophy of the endothelial and vascular smooth muscle cells and also a buildup of lipids at the suprachoroid.

Wong et al[37] noted that the subfoveal choroid was thicker in patients with hypercholestremia

Blood pressure:

Maul et al[38] found that there was a correlation between increased diastolic blood pressure and choroidal thickness. He stated that increased diastolic blood pressure may cause increased choroidal blood flow which caused an increase in choroidal thickness. Reiner et al[39] in his study noted that as the blood pressure declined there was a notable decrease in the choroidal blood flow.

General factors:

Age:

Choroidal thickness decreases with age. This is because there is a reduction in the number increase in choroidal blood calibre of vessels thus contributing to the decrease in thickness.[16]

Spaide et al[4] in his study showed that there is a decrease in choroidal thickness by 15.6 micrometers with each decade of life. This negative correlation of choroidal thickness with age may play a role in the pathogenesis of age related eye diseases.

Diurnal variation:

Studies have proved there is significant diurnal variation in choroidal thickness.

In his study Tan et al[40]measured choroidal thickness at 5 time points during daytime and found significant diurnal variations in choroidal thickness. They found that choroidal thickness was thickest during early morning and decreased as the day passed and was thinnest at around 5PM.

THERAPEUTIC:

Pan -Retinal photocoagulation:

In Pan retinal photocoagulation the retinal pigment epithelium is the main site of heat absorption. The heat dissipated from the retinal pigment epithelium cells causes damage to the outer retina and choroid. The damaged choroid failed to reperfuse thus becoming fibrosed leading to thinning of choroid.[34]

Studies have shown the effect of choroid at 1 week and 3 months post pan retinal photocoagulation. Cho et al[41] measured choroidal thickness in patients 1 week post PRP where he found the choroidal thickness to be increased. The increase in thickness was attributed to increase in choroidal

blood flow due to vasodilatation or choroidal effusion induced by possible choroidal vascular obstruction by the laser photocoagulation .

Unsal et al[42] measured choroidal thickness 3 months post PRP where he found that the choroid was thinner.

Intravitreal Injections:

Studies[43-44]have shown that there is a reduction in the thickness of the choroid following intravitreal injections. It was postulated that anti VEGF penetrates all layers of retina and accumulates in the choroidal vessel wall .Anti VEGF causes constriction of choroidal vessels and decrease in choriocapillaris causing thinning of the choroid.

Ocular Causes:

Myopia:

Choroidal thickness is decreased in high myopes. Fujiwara et al [45] stated that Choroidal thickness decreases as age advances and this may play a role in choroid atrophy and the pathogenesis of decreased vision in high myope.

They also state that although both retina and choroid are thinned in high myopia, choroid may still be able to supply the thinned retina with adequate oxygen and nutrients.

Spaide et al[4] showed that for every ten years of life subfoveal choroidal thickness decreased by 12.7 micrometers .The Choroidal thickness (CT) also decreased by 8.7 micrometers for increase in each diopter of myopia. This was important as it suggested that abnormality of the choroid may play a role in the pathology of myopic degeneration.

Glaucoma:

Yin et al[46] proposed in his study on 25 postmortem Primary open angle glaucoma eyes and 18 age matched normal eyes found that choroid was 50 micrometers thinner.

The choroidal thinning was associated with vessel loss occurring mostly the inner choroidal level. It was also found that there was an overall reduction in the diameter of the vessel.

Cataract surgery:

Pierru et al[47] in his study of 115 eyes of 95 patients who had undergone phacoemulsification has shown that there is an increase in choroidal thickness. The choroidal thickness was more in post operative day one and seven.

The increase in choroidal thickness was attributed to the release of prostaglandins in the anterior chamber where it caused blood aqueous barrier to breakdown resulting in the pro–inflammatory mediators accumulation which moved into the posterior segment and caused inflammation in the retina by breakdown of inner blood retinal barrier. There was also increase in the permeability of perifoveal capillaries.

Choroidal pathology:

Central serous chorioretinopathy:

Imamura[48] in his study comprising of 19 patients with central serous chorioretinopathy proved that there was a significant increase in choroidal thickness. This increase was attributed to the increase in hydrostatic pressure of the choroid

Age related macular degeneration:

In his study on choroidal thickness in age related macular degeneration Manjunath et al[49] noted that the choroidal thickness increases in some eyes and decreases in others.

It was found that in Age related macular degeneration there was a reduction in choroidal blood flow and it further decreased as the disease progressed. The decreased flow was attributed to multiple factors:

choriocapillary narrowing, loss of cellularity and choroidal thinning especially in the choriocapillaris. Vasoconstriction and hypoxia also happens due to increased levels of nitric oxide.

Choroidal atrophy:

In his study Spaide et al[4] established a new clinical entity, Age related choroidal atrophy where he found that the subfoveal choroidal thickness was reduced as well as nasally. All the patients in that particular study group were also found to have a tessellated fundus appearance. It was also found that the choroidal vessels sub foveally in those patients were also reduced thus having a negative influence on vision.

Retinitis Pigmentosa:

Retinitis pigmentosa there is a primary vascular dysfunction including reduced choroidal as well as retinal blood flow which leads to photoreceptor damage. Research has shown that the eyes with retinitis pigmentosa tend to have a choroid which is thinner (both focal and diffuse thinning is present).

OPTICAL COHERENCE TOMOGRAPHY:[50]

Introduction:

It is new diagnostic essential tool which can perform cross sectional imaging of biologic tissues.

In ocular tissues, it helps greatly invivo analysis of retinal tissue for diagnosis and management of retinal disorders and other conditions like glaucoma.

Principles of OCT:

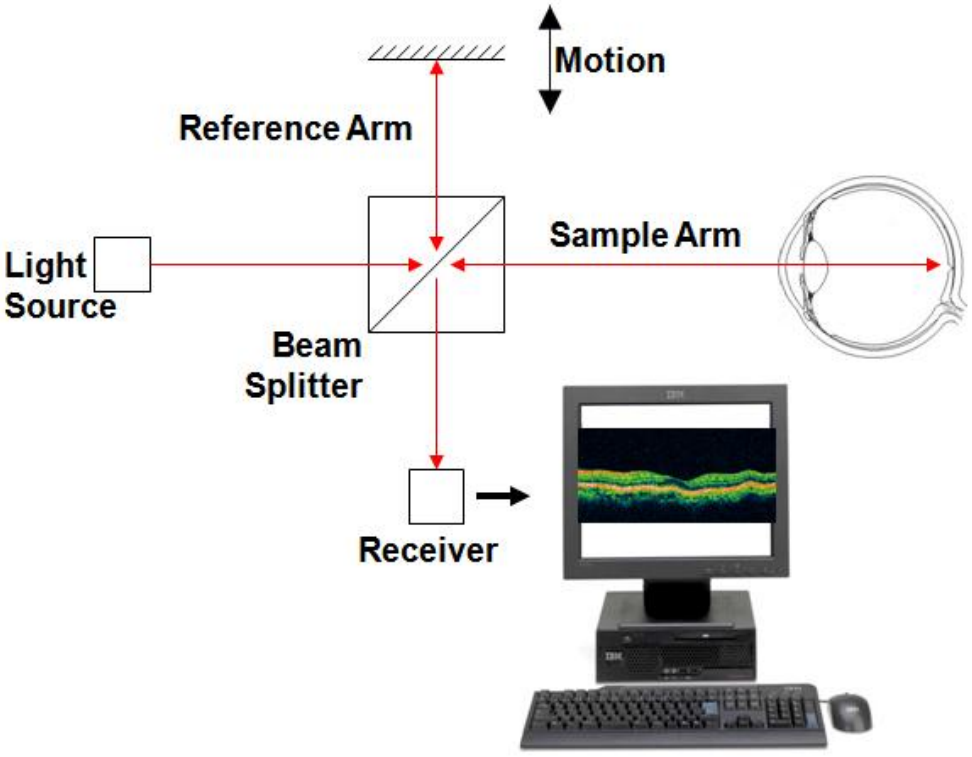


FIG 17. PRINCIPLE OF OCT

It is a technique to detect differences between two (interfering) or more superimposing waves.

Interferometry works in such a way that two waves with the same frequency and having similar phase will add each other. In the same principle two waves with opposite phases will subtract.

Light from a source is directed onto a partially reflecting mirror and is split into a reference and a measurement beam.

The measurement beam is reflected from the specimen with different time delays according to its internal microstructure.

A variable time delay is produced when the light in the reference beam is reflected from a reference mirror at a variable distance.

Multiple echoes from the specimen and a single echo from the reference mirror at a known delay are combined and detected

The detected signal contains information on the position of the scatters within the sample, on their reflectivity, velocity and polarization properties. By this collection of depth scans from the sample three dimensional construction of cross-sectional images is possible.

Evolution of OCT:

Time domain OCT:

Here a reflected beam of light is compared to a beam of light from a moving reference mirror wherein time delay between the two beams can be measured .

Features:

A – Scan generated sequentially one pixel at a times of 1.6 seconds.

Moving reference mirror 400 scans/second

Resolution -10 micron

Slower than eye movement.

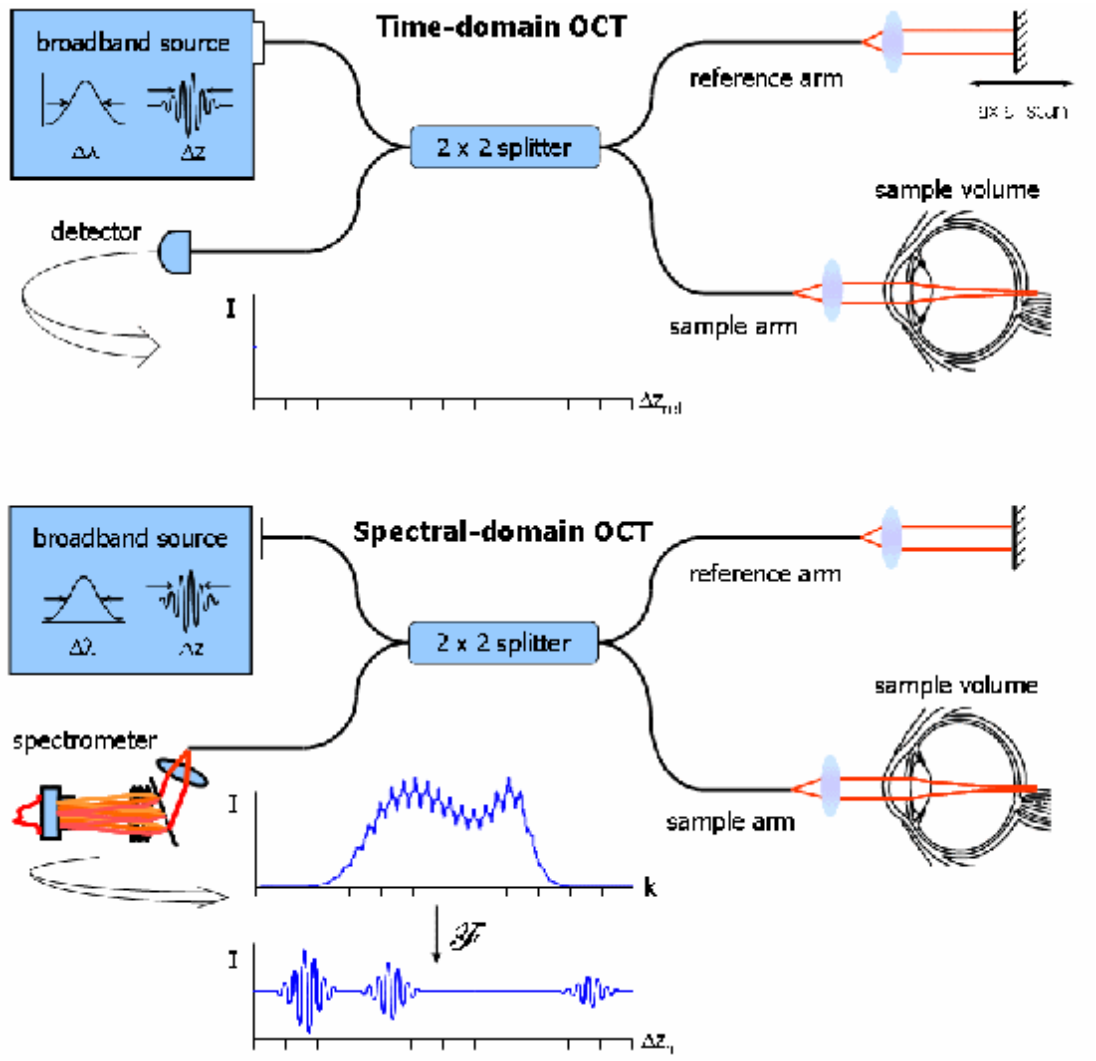


FIGURE 18. TIME DOMAIN AND SPECTRAL DOMAIN OCT

Spectral Domain OCT:

Here a spectrometer is used in place of a single detector. The difference in wavelength between the light from the fixed reference arm and that returning from the tissue is measured using a spectrometer.

In Spectral domain OCT there is no movement of the reference arm and instead the reflected light is analysed using a spectrometer. The wavelength of the light source is 840 nm.

The immediate advantage of the technology is the high number of scans required per second –approximately 27,000 A-scans per second making true three dimensional imaging possible.

Advantages of Spectral domain OCT:

1. Simple
2. Reliable
3. Sensitive (resolution of 5 microns)
4. Reproducible

Swept Source OCT:

The source laser rapidly sweeps across the spectral frequency band. At the beam splitter the reflected signals from the sample and reference arm

(fixed) are combined and directed at the detector after which an axial scan is constructed from depth resolved spectral interference signals.

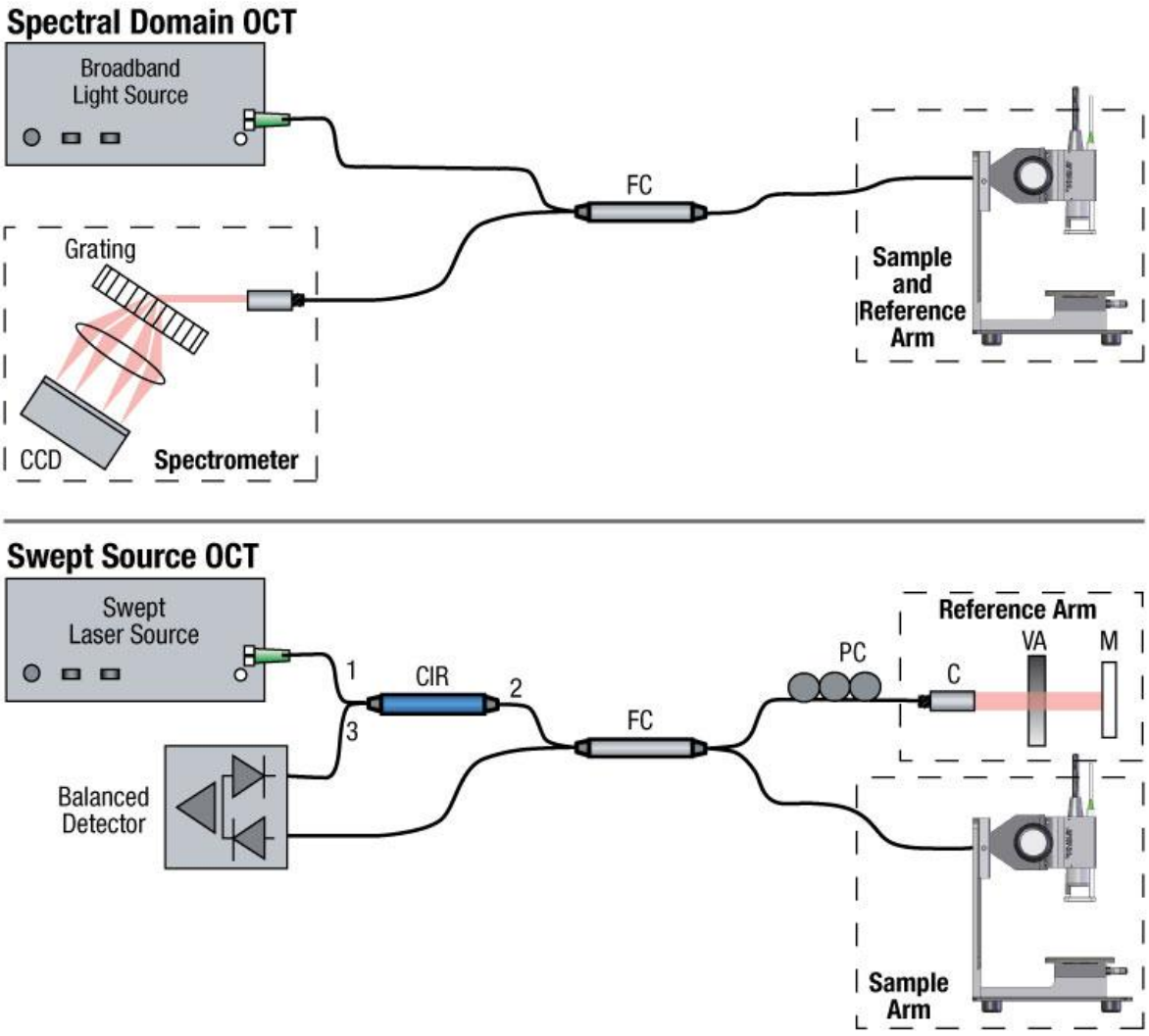


FIG 19. SPECTRAL DOMAIN AND SWEPT SOURCE OCT

Enhanced depth imaging OCT:[4]

FIG 20. HEIDELBERG SPECTRALIS OCT

EDI was pioneered by ophthalmologists Ron Margolis, MD, and Richard F. Spaide, MD, in 2009. Before their work, it was impossible to visualize the choroid by OCT because of:

1. The pigmented RPE acted as a barrier because of which penetration of light was poor.
2. Light scatter by the choroidal vasculature itself.

Using the Spectralis (Heidelberg Engineering), Dr. Margolis and Dr.Spaide found that they could more effectively view the choroid by inverting the image. Originally, they accomplished this by simply positioning the patient slightly closer to the machine. By convention, the zero delay line is located at the top of the imaging screen and represents the area of most precise focus. By inverting that image, the chorioscleral interface is placed near the zero delay line, improving the scan quality of the deeper, posterior structures. EDI-OCT penetrates an additional 500µm to 800µm deeper compared with traditional OCT imaging.

Applications of OCT:

- Retinal profiles seen with OCT:
- Normal profile
- Enlarged foveal depression
- Decreased foveal depression
- Asymmetric foveal depression
- CSCR
- ARMD
- Diabetic Retinopathy
- Macular Hole
- Treatment of epiretinal membrane

- To assess treatment response in glaucoma patients by analysing ONH and NFL thickness.

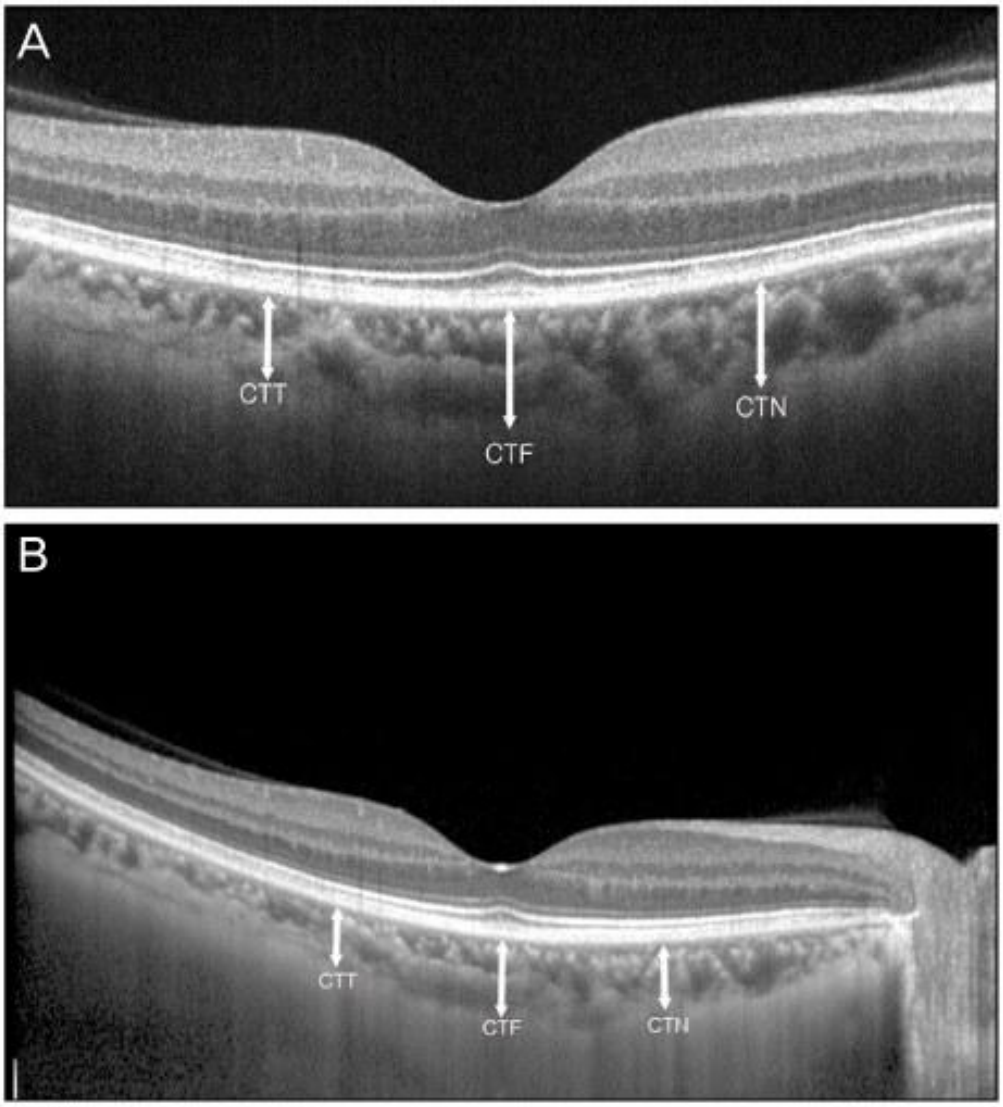


FIG 21. CHOROID MEASURED FROM HYPEREFLECTIVE RPE TO THE CHORIOSCLERAL INTERFACE

Measurement of choroid using EDI OCT:

Choroid is measured from the hypereflective Retinal pigment epithelium to the chorioscleral interface.[4,34,35] The choroid is thicker under the fovea and is thinner nasally than temporally. Choroidal thickness measurements in normal subjects appear to be highly reproducible.

REVIEW OF LITERATURE:

1.) Choroidal thickness in Patients with Diabetic retinopathy: Unsal et al ,2014

Retrospective cross sectional research where 151 eyes from 8o patients with DR and 40 eyes of 20 healthy individuals. The DR patients were grouped into, Mild – moderate NPDR with Macular oedema and proliferative diabetic retinopathy.

Choroidal thickness was measured using an optovue RTVue 100-2. They came to a conclusion that Choroidal thickness was found to be significantly decreased in DME (206.8 micrometers) and PDR (203.8 micrometers) groups when compared with normal group (259 micrometers)

2.) Choroidal thickness profile in healthy Indian subjects: Chhablani et al ,2014

In this first study of choroidal thickness in Indian population, 211 eyes of 115 healthy subjects participated were involved.

Cirrus HD OCT was used to measure the choroidal thickness from RPE to the chorioscleral interface at junctions of 500 micrometers nasally and temporal to fovea for about 3000 micrometers.

The study concluded that Subfoveal choroid was the thickest and nasal being the thinnest. It also stated that age is a critical factor which has a negative correlation to choroidal thickness.

3.) Measurement of subfoveal choroidal thickness after cataract surgery in enhanced depth imaging optical coherence tomography. Pieurru et al ,2014

This study compared the sub-foveal choroidal thickness before and after phacoemulsification. Measurement of the subfoveal choroidal thickness in 95 patients were performed preoperatively and 1 day , 7 days ,1 month and 3 months postoperatively.

They concluded that choroidal thickness was found to be increased under the fovea after cataract surgery. They also found that the changes were greater in pseudophakic cystoid macular oedema cases.

4.) Changes of choroidal thickness after treatment for Diabetic retinopathy: Lee et al ,2014

This study included 31 eyes in the intravitreal bevacizumab group and 31 patients in the PRP group and 35 eyes in the intravitreal and PRP group.

In this study Enhanced depth imaging was done one month before each treatment to measure subfoveal and extrafoveal choroidal thickness. The BCVA and central macular thickness was also measured.

They came to a conclusion that choroidal thickness was significantly decreased in all group but there was no significant change among the three groups. The subfoveal choroidal thickness and Central macular thickness were significantly reduced after Intravitreal bevacizumab and Intravitreal – PRP group.

5.) Analysis of morphological features and vascular layers of choroid in diabetic retinopathy using spectral domain optical coherence tomography:Adhi et al, 2013

This study was a cross sectional retrospective review. 33 eyes of patients with DR and twenty four eyes of twenty four controls participated in this study. Subjects were split into 3 groups : NPDR with DME, PDR with DME and DME alone.

Spectral domain OCT (cirrus-HD) was used for measuring the choroidal thickness.

They concluded that Sub foveal choroidal thickness, subfoveal medium choroidal vessel layer and choriocapillaris thickness were reduced markedly in Proliferative DR , Diabetic Macular oedema.

6.) Changes in choroidal thickness in relation to severity of retinopathy and macular oedema in type 2 diabetic patients, Kim et al 2013

In this study 235 eyes from 145 patients ,195 eyes which had no ocular treatment and 40 eyes with prior history of PRP done for PDR were divided into no DR, Mild/Moderate nonproliferative DR (NPDR) ,severe NPDR ,PDR and PRP treated eyes.

The CT was measured using the Heidelberg spectralis OCT. They came to a conclusion that the choroid was significantly thicker in DME than other DR groups and that the severity increased as it progressed from Mild NPDR to PDR and the choroid was thinner in PRP treated eyes.

7.) Changes in Sub foveal choroidal thickness after argon laser panretinal photocoagulation: Cho et al, 2013

A prospective comparative case series where subfoveal choroidal and macular thickness was measured one week post pan retinal photocoagulation (after 3 sessions) using enhanced depth imaging spectral domain –OCT.

28 eyes of 21 patients with severe diabetic retinopathy were involved in this study. Pre and post PRP (1 week) choroidal and macular thickness were measured.

They concluded that there was an increase in subfoveal choroidal thickness. There was no correlation with changes in macular thickness.

8.) Choroidal thickness in relation to hypercholesteremia on enhanced depth imaging optical coherence tomography: Wong et al, 2013

A cross sectional observational study. A total of 322 eyes of 161 subjects were analysed. The subjects were divided into those having hypercholestremia and normal control subjects. Choroidal thickness was measured using Heidelberg software at 4 locations (1mm superior, inferior, nasal and temporal) to the fovea.

They concluded that choroidal thickness was significantly higher in Patients with hypercholestremia (306 micrometers) than normal subjects (258 micrometers).

9.) Choroidal thickness in patients with diabetic retinopathy analysed by spectral Domain optical coherence tomography:Regatieri V et al ,2012

In this study 49 eyes of 49 Diabetic retinopathy patients and 24 aged matched normal subjects were taken. They were split into 3 groups:

Mild –moderate DR with no DME, Mild –Moderate DR with DME and treated Proliferative DR without DME.

The choroid was measured using spectral domain OCT from the posterior edge of the retinal pigment epithelium to the chorio-scleral interface.

They concluded that choroidal thickness is altered according to the grade of retinopathy. Choroidal thickness is significantly reduced in the presence of DME.

10.) Diurnal Variation of choroidal thickness in Normal, healthy subjects measured by spectral domain optical coherence tomography:Tan et al, 2012

A prospective study of 12 healthy individuals where each of them underwent sequential ocular imaging at five fixed two hour time intrevals. They concluded that the choroidal thickness was more in the morning and is correlated with age, axial length refractive error and changes in systolic pressure.

11.) Analysis of choroidal thickness in age related Macular degeneration using spectral domain optical coherence tomography; Manjunath et al, 2011

In this cross sectional retrospective study 47 patients with wet and dry age related macular degeneration were included in this study. Choroidal thickness was measured by two independent observers .

They concluded that the patients with AMD may show variable choroidal thickness. They also stated that it was unclear why the choroid was thinner in certain eyes and vice versa.

12.) Enhanced depth imaging optical coherence tomography of choroid in central serous chorioretinopathy ;Imamura et al ,2009

This study evaluated the choroidal thickness in patients with central serous chorioretinopathy.

In this study 28 eligible eyes of 19 patients with Central serous chorioretinopathy underwent EDI –OCT. The subfoveal choroid was measured from the hyperreflective RPE to the inner scleral border.

It was found that the choroid was significantly thickened (505 micrometers)

13.) Enhanced Depth Imaging Optical Coherence Tomography of the Choroid in Highly Myopic Eyes: Fujiwara et al, 2008

This study measured macular choroidal thickness in highly myopic eyes using EDI –OCT were obtained by positioning a spectral domain OCT device close enough to the eye to acquire an inverted image. Choroidal thickness was measured from outer border of the RPE to the chorioscleral interface. The temporal and nasal choroidal thickness was measured at 100

micrometers intrevals of a horizontal section 3mm temporal and 3mm nasal to the fovea.

They concluded that the choroid in highly myopic eyes is thinner and undergoes further thinning with age and degree of myopia. They also postulated that abnormalities of the choroid may play a role in the pathology of myopic degeneration.

14.) Widespread choroidal insufficiency in Primary Open angle glaucoma;1997

This study investigated choroidal perfusion in glaucoma using histological and angiographic techniques.

In this study choroidal vasculature in 25 cases of Primary open angle glaucoma was examined with clinicopathalogical studies. Choroidal thickness was measured at fixed distances from the disc margin using light microscopy.

The study concluded that choroid was significantly thinner (50 micrometres thinner) in glaucoma than in normal patients.

15.) Choroidal thickness measured by spectral domain optical coherence tomography:Factors affecting thickness in glaucoma patients; Maul et al, 2011

A cross sectional study to measure choroidal thickness in 74 glaucoma and glaucoma suspects using EDI-OCT

It was concluded that the macular choroid was significantly thinner in association with 4 features like longer eyes, with age, lower diastolic perfusion pressure and thicker central corneas.

16.) Alterations in the choroid in hypercholestremic rabbits: Reversibility after normalization of cholesterol levels. Salazar et al,2007

This study evaluated the effect of choleseterol in rabbits who were fed with cholesterol enriched diet for 8 months.

It was found that the choroidal thickness was more in hypercholestremic rabbits and that the choroidal changes were irreversible once the cholesterol levels were controlled.

17.) Choroidal Blood Flow Compensation in Rats for Arterial Blood Pressure Decreases is Neuronal Nitric Oxide-Dependent but Compensation for Arterial Blood Pressure Increases is not; Reiner et al

In this study, Reiner et al investigated whether Choroidal Blood flow can compensate for increases and decreases in Arterial Blood Presuure in rats. Choroidal Blood flow was continuously monitored using laser Doppler flowmetry in anesthetized rats, and Arterial blood pressure was measured through the femoral artery. Choroidal blood flow and arterial blood flow were sampled at multiple intervals over a 2-4 hour period during which ABP varied freely, and the results compiled across rats.

Choroidal Blood Flow was found to be near baseline over an ABP range from 40 mmHg above basal ABP (90-100 mmHg) to 40 mmHg below basal ABP. Choroidal blood flow largely followed ABP linearly below 60 mmHg. As BP increased above 100 mmHg , choroidal vascular resistance increased linearly and decreased linearly as BP declined from basal to 60 mmHg. But resistance declined no further below 60 mmHg. Inhibition of nitric oxide (NO) formation by either a selective inhibitor of neuronal nitric oxide synthase (NOS) (N ω-propyl-L-arginine) or a nonselective inhibitor of both neuronal NOS and endothelial NOS (N ω-nitro-L-arginine methyl ester) did not affect compensation above 100 mmHg ABP. But ChBF

linearly follow declined as BP fell below 90 mmHg. In NOS-inhibited rats, with BP above 100mmHg, choroidal vascular resistance increased but remained at baseline below 90 mmHg.

18.) Effects of a human VEGF antibody (Bevacizumab) on deprivation myopia and choroidal thickness in the chicken; Mathis et al ;2014

This study was done to study the effect of Bevacizumab on choroidal thickness and deprivation myopia in chicken.

It was found that:

1.) Following a single unilateral intravitreal injection of 0.5 mg bevacizumab, it partially suppressed the development of deprivation myopia, similarly in both eyes.
2.) Bevacizumab completely suppressed choroidal thickening that normally occurs when eyes recover from induced myopia over a time period of about 10 days
3.) Beavacizumab had little effect on the choroidal thickness in eyes that had normal visual experience
4.) VEGF-A was absent in sclera. But it was found to be highly expressed in the walls of choroidal blood vessels and presumed nerve

fiberbundles. It was also found in retinal photoreceptors and cells of the inner and outer nuclear layer.

In conclusion, Bevacizumab is equally effective in human and chicken tissue, has similar time constants (few days), has almost symmetrical effects on myopia in both eyes even after ocular application in only one eye. It was also found that it fully suppresses choroidal thickening that normally follows during recovery from deprivation myopia.

AIMS AND OBJECTIVES

AIM:

To measure and compare the subfoveal choroidal thickness in various stages of Diabetic retinopathy and normal participants using enhanced depth imaging optical coherence tomography

OBJECTIVES:

To measure and compare the subfoveal choroidal thickness in various stages of Diabetic retinopathy with normal participants and to correlate the subfoveal choroidal thickness with severity of DR.

MATERIALS AND METHODS

This study was conducted with the approval of the local ethics committee Abiding the tenents of the declaration of Helsinki. Study Period : December 2014 – May 2015

All the patients included in this study [21 diabetic patients (42 eyes) and 46 eyes of 25 control patients)] underwent complete ophthalmic examination including refraction ,best corrected visual acuity and Intraocular pressure measured by non contact tonometry. The patient underwent dilated 90 dioptre slit lamp examination and Diabetic retinopathy grading was done using the ETDRS classification. The patients were split into Mild –Moderate NPDR, Severe NPDR, PDR ,CSME groups.

All known cases of Diabetes mellitus on treatment were included in this study. Exclusion criteria included patients with other systemic illness ,previous history of intravitreal injections or PRP, High myopia (more than -3 diopters) hypermetropia more than +3 diopters, Factors affecting choroid like (age related macular degeneration ,central serous chorioretinopathy, polypoidal choroidal vasculopathy), glaucoma and patients who underwent cataract extraction beyond 6months. All patients underwent EDI – OCT. Patients where the choriosclera interface was less than grade 1 were not included in the study.

INCLUSION AND EXCLUSION CRITERIA:

INCLUSION CRITERIA	EXCLUSION CRITERIA
Type 2 Diabetes mellitus	Hypertension, Hypercholestremia, Renal failure
Media where the posterior segment is clearly visible	High myopia (more than -3 D), Hypermetropes (+3 D)
	choroidal pathology, Glaucoma
	History of ocular surgeries, Intravitreal inj or LASER

INSTRUMENTATION:

All choroidal thickness measurements were done using the SPECTRALIS HRA + OCT platform (Heidelberg Engineering Inc, Heidelberg, Germany). All patients also underwent Auto fluorescence and fundus photography.

SPECIFICATIONS :

Light source	ICG excitation: Diode laser, wavelength 790 nm,laser class 1 IR reflectance: Diode laser ,wavelength 820 nm, Laser class 1 FA excitation and Blue reflectance: Solid state laser ,wavelength 488 nm, laser class 1 Super luminescence diode (SLD) average Wavelength 870 nm ,LASER class 1
Scanning LASER Specifications	Transverse field of view Scan angle: 30°x30°, 20°x20°, 15°x15° Wide field composite image to 120° High speed mode Digital image size: 768x768 / 512x512 / 384x384. High resolution mode Digital image size: 1536x1536 / 1024x1024 / 768x768. Scan time per image: 192 ms / 128 ms / 96ms. Lateral resolution 5 μm/pixel digital Image Acquisition Frequency 5 Hz / 7 Hz / 9 Hz Maximum Scan Depth 8 mm
OCT scanner specifications:	A-Scan scan rate: 40 KHz Scan depth :1.8 mm Scan size: 512 pixels axial resolution: 7 micrometre optical B-scans scan angle:30/15/10 degree Scan width : upto 9mm High speed mode scan width :768 A-scan Acquisition time: 19 ms scan rate : 48 B scans /sec High resolution mode scan width: 1,536 A-scan
Focus adjustment range	-12 diopters to +12 diopters spherical

IMAGING PROTOCOL:

The same clinician performed EDI-OCT imaging of all subjects in the morning (between 9 am and 4pm) with Heidelberg Spectralis equipment (Heidelberg Engineering Inc, Heidelberg, Germany).

PROTOCOL FOR CHOROIDAL THICKNESS MEASUREMENT:

Scan Angle: 30°X15°

Sections : 19

ART: 100

Mode: Enhanced-Depth imaging

HIGH-RESOLUTION MODE

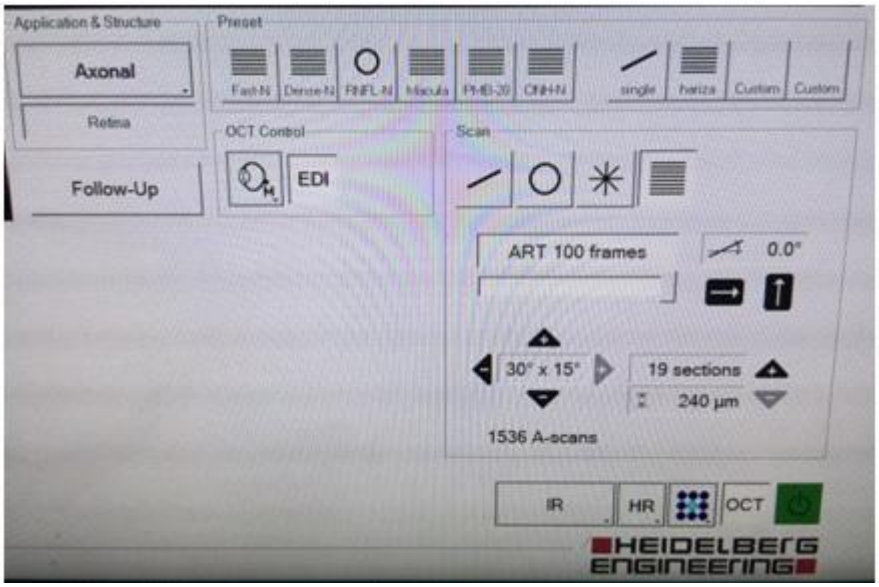


FIG 21. PARAMETERS FOR EDI OCT

Subfoveal choroidal measurement:

The subfoveal choroid is measured from the Hyper-reflective line of the RPE-Bruch's membrane complex to the chorioscleral interface which forms the posterior boundary. The region of the centre of the fovea was identified as the area of maximum depression.

The parafoveal nasal and temporal measurements were done at 500 micrometres on each side from the centre of the fovea. The choroidal thickness was measured using the caliper tool available in the Spectralis platform.

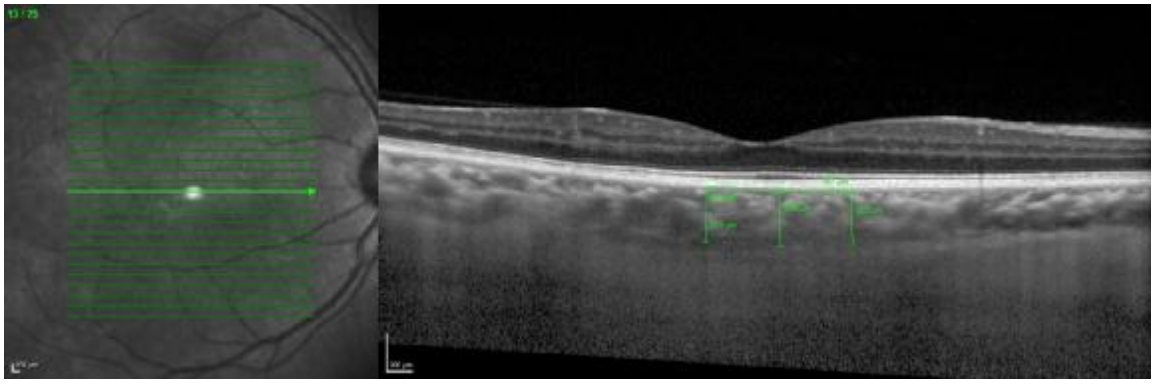
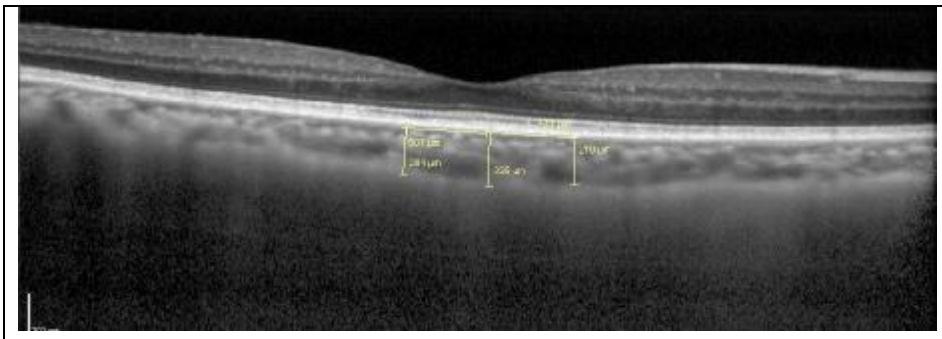
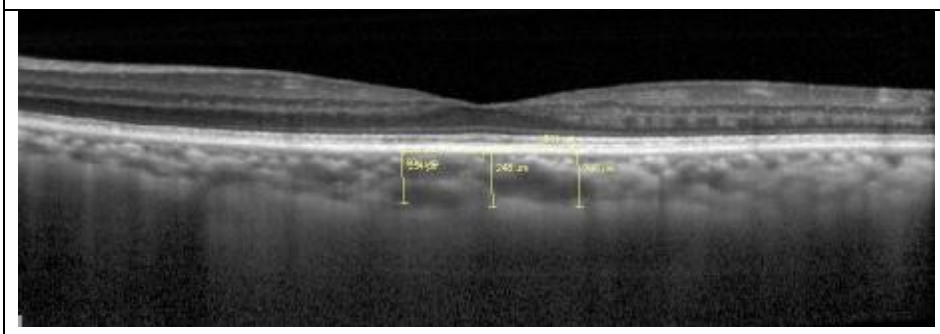
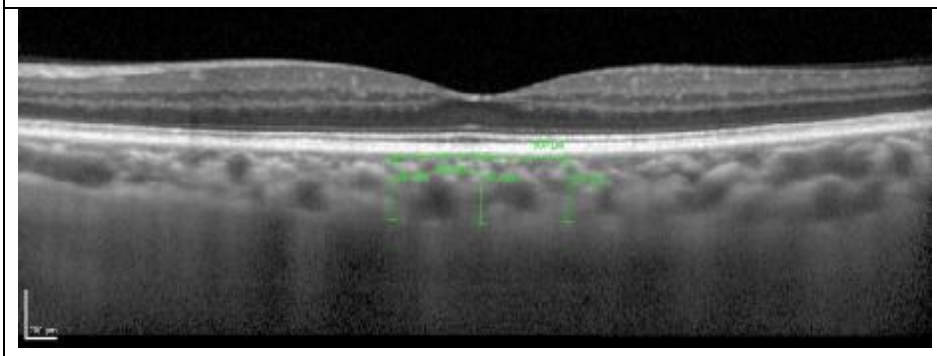
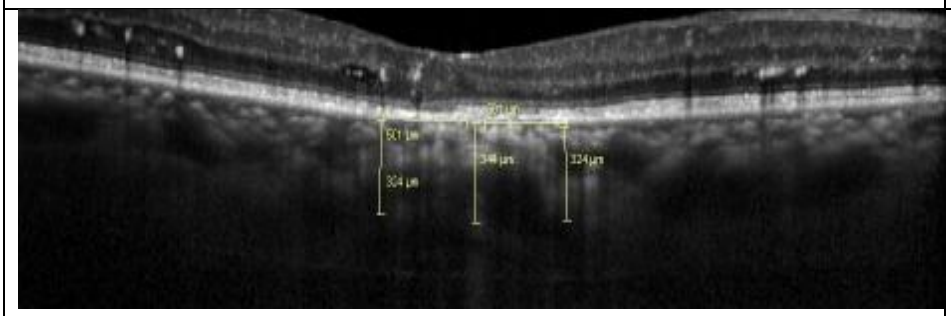


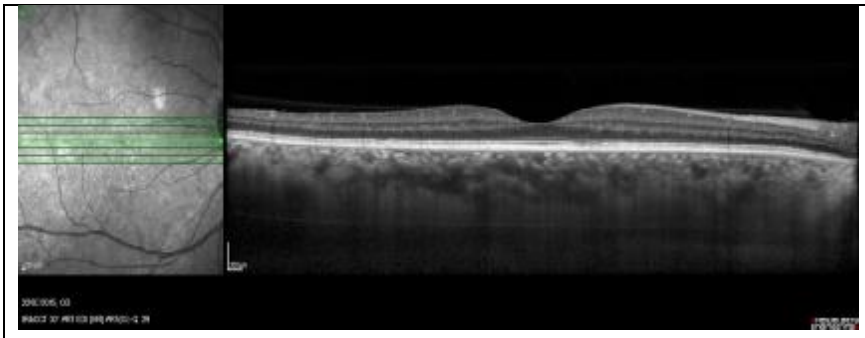
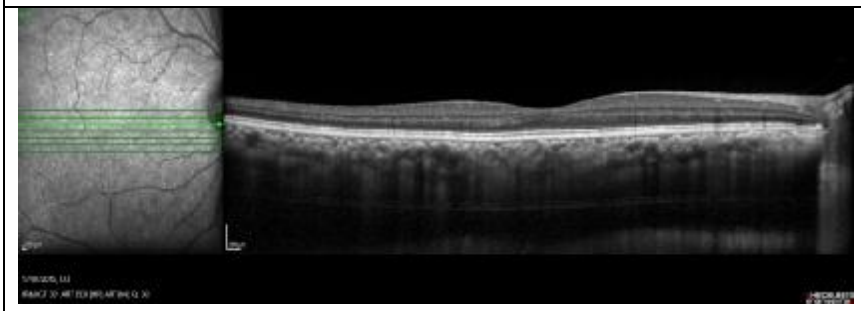
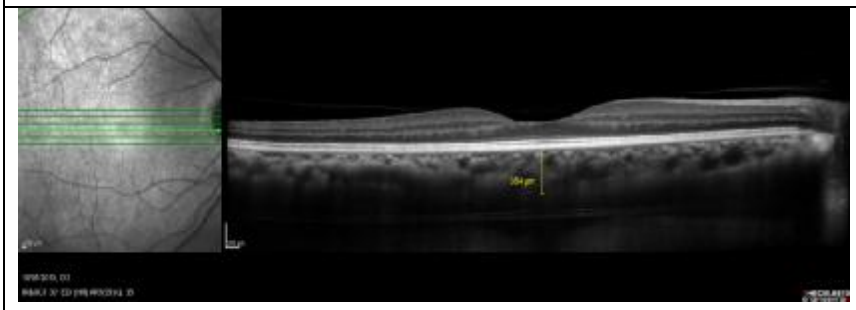
Fig 22. EDI OCT MEASUREMENT OF A DIABETIC EYE.

	**MILD NPDR**
	**MODERATE NPDR**
	**SEVERE NPDR**
	**PDR**

SUBFOVEAL CHOROIDAL THICKNESS MEASUREMENT IN VARIOUS STAGES OF DR

Chorioscleral interface grading:

All OCT images were graded into four categories based on the visibility of the chorioscleral interface along the entire length of the scan. OCT images with signal strength less than 6 dB and CSI grade less than one were excluded from study

	Grade 1: 25% of CSI seen
	Grade 2: 25-50% CSI seen
	Grade 3: 50 -75% seen
	Grade 4: >75% seen

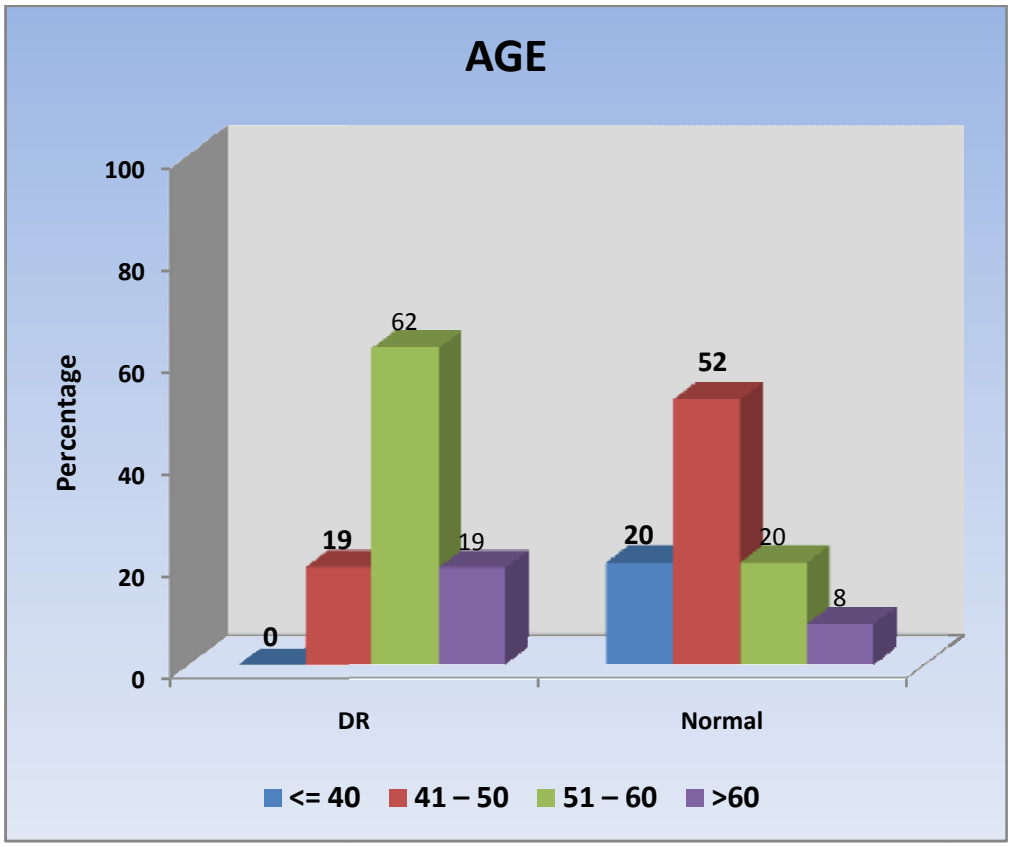
STATISTICAL ANALYSIS

AGE

Group	n	Mean(SD)	Min – Max	P-value
Diabetic retinopathy	21	56.05(4.7)	49 – 65	0.0001
Normal	25	47.24(8.3)	33 – 67	

Age Category	DR	Normal	Total
<= 40	-	5(20.0)	5(10.9)
41 – 50	4(19.0)	13(52.0)	17(37.0)
51 – 60	13(61.9)	5(20.0)	18(39.1)
>60	4(19.0)	2(8.0)	6(13.0)
Total	21	25	**46**

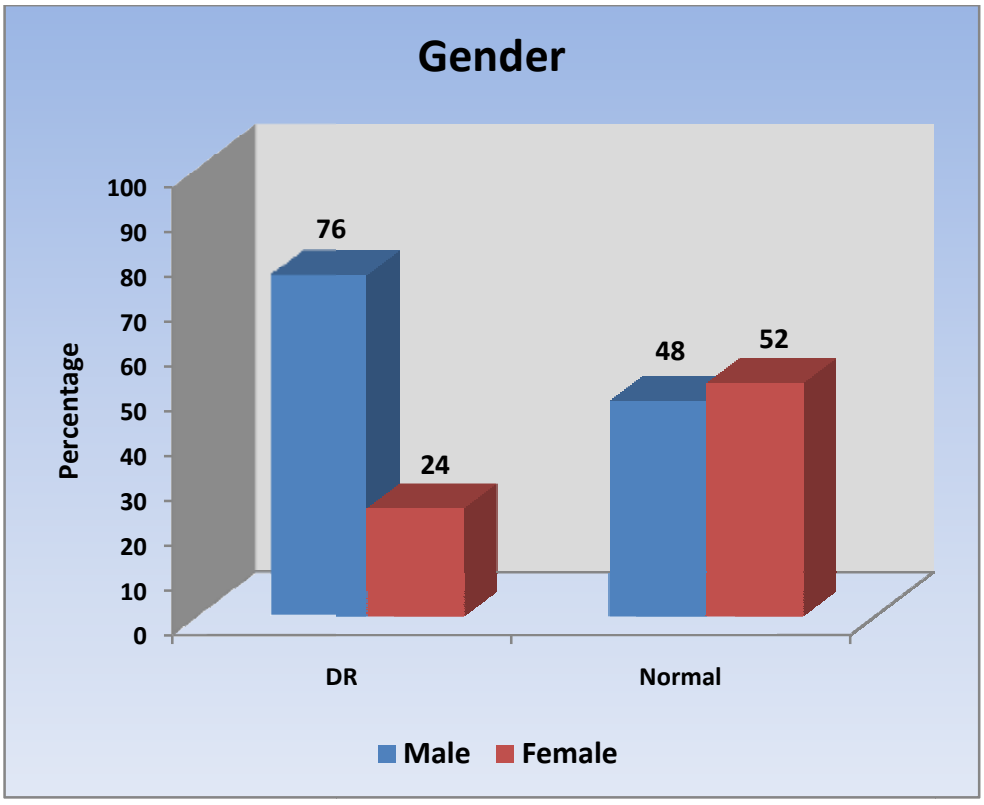
Mean age was higher in Diabetic Retinopathy group compare to normal group, it was also statistically significant difference (P-value = 0.0001, using t-test). Also 62% of the patients were 51 – 60 age limits in DR group and 52% of the patients were 41-50 age limits in normal group.


AGE
Percentage
100
80
60
40
20
0
0
19
62
19
20
52
20
8
DR
Normal
<= 40
41 – 50
51 – 60
>60

GENDER

Gender	Group		Total (n=46 patients)	P - value
	Normal (n=25 patients)	*Diabetic Retinopathy (n=21 patients)*		
Male	12(48.0)	16(76.2)	28(60.9)	0.051
Female	13(52.0)	5(23.8)	18(39.1)	

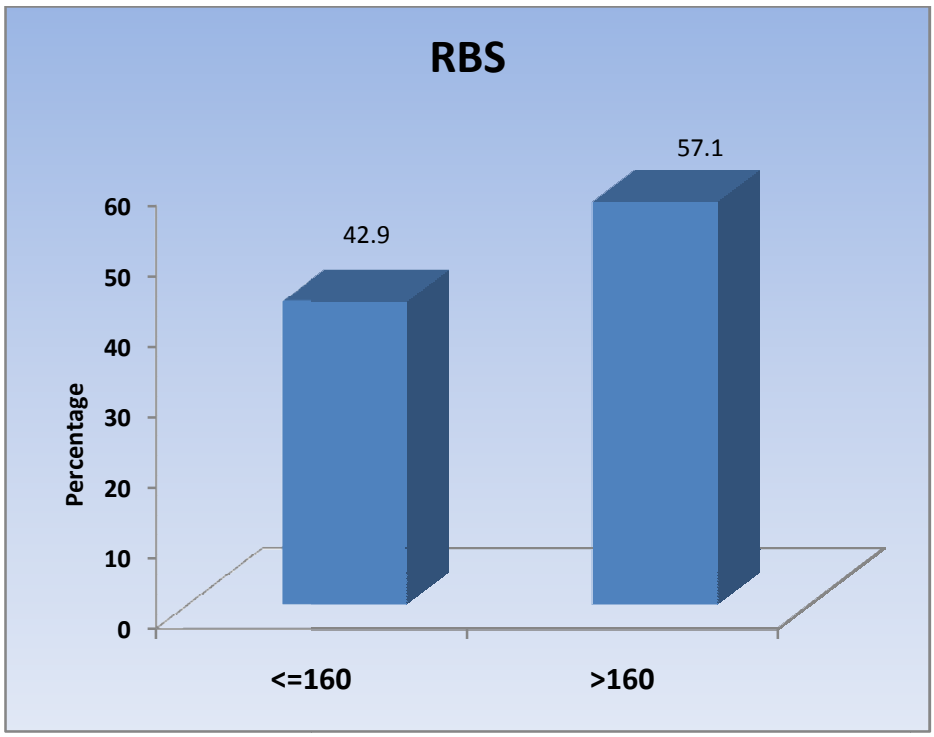
48% of the patients were male in Normal group and 76% of the patients were male in DR group. It was not showing statistically significant difference between groups (P-value = 0.051, using chi-square test).



RBS

The Mean (SD) of RBS is 196.76(84.64)mgs% & its range is 101 - 375 mgs%. 12(57%) patients had more than 160 RBS level in DR group.

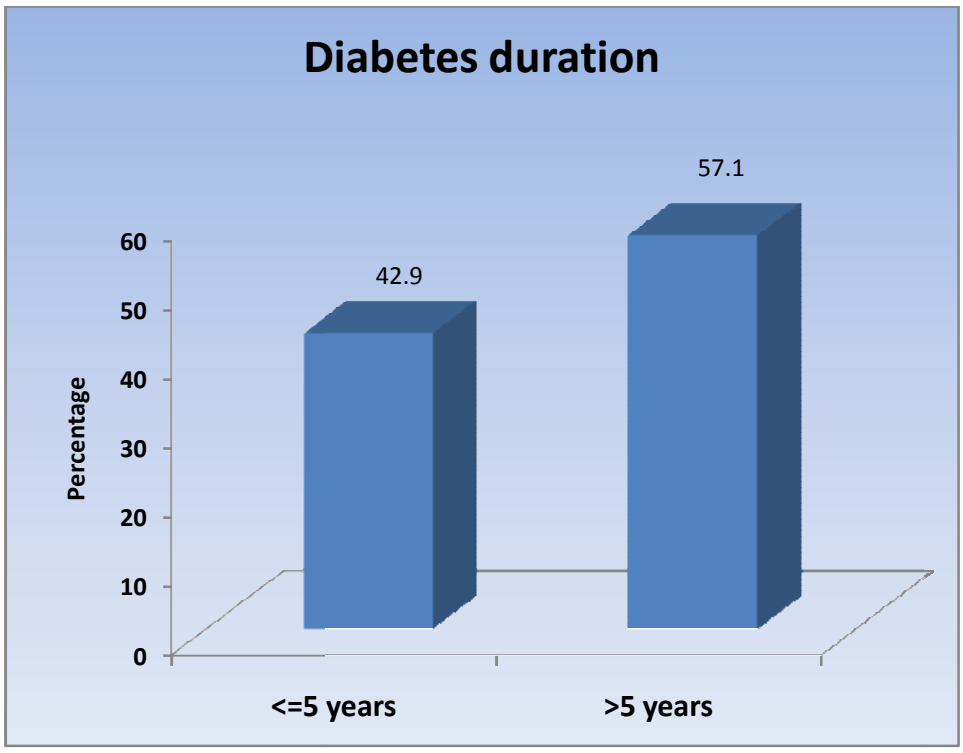
RBS	n	%
<= 160	9	42.9
> 160	12	57.1
Total	**21**	**100**



DURATION OF DIABETES

The Median of Duration of Diabetic is 7 years & its range is 15 days - 13 years. 12(57%) patients had more than 5 year diabetes in DR group.

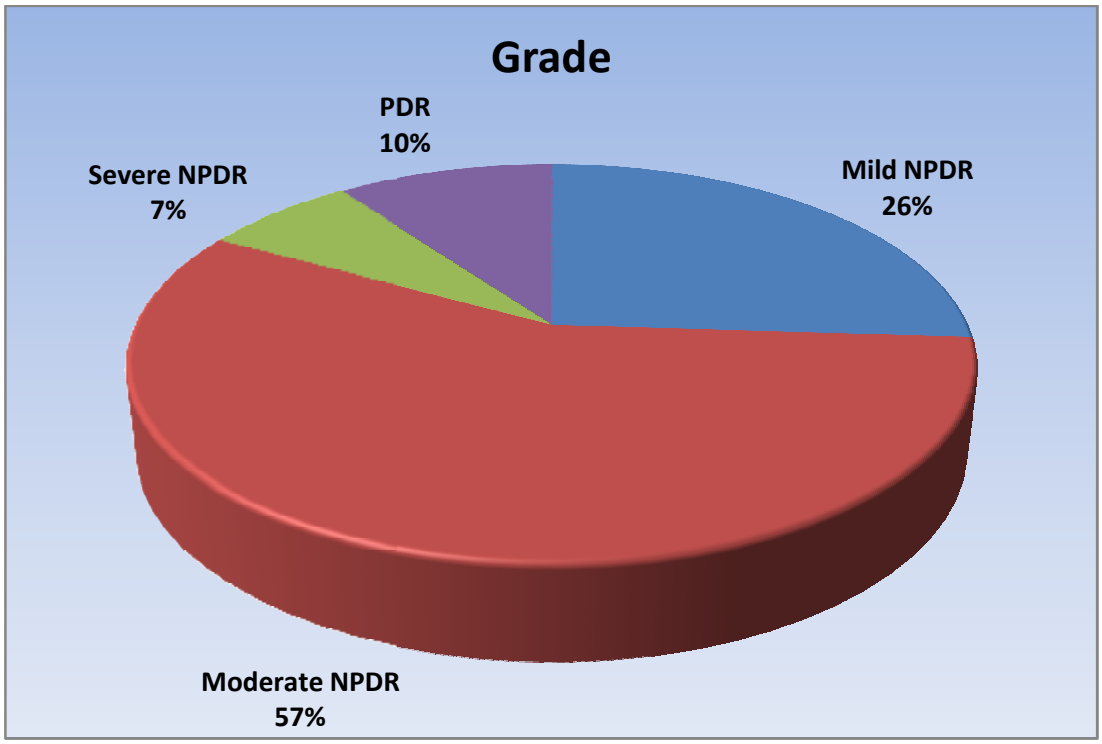
Duration of Diabetic	n	%
<= 5 years	9	42.9
> 5 years	12	57.1
Total	**21**	**100**



GRADE OF DR

Grade of DR	**n**	**%**
Mild NPDR	11	26.2
Moderate NPDR	24	57.1
Severe NPDR	3	7.1
PDR	4	9.5
Total	**42**	**100**

26% of eyes had mild NPDR, 57% of eyes had moderate NPDR, 7% had Severe NPDR and 9.5% had PDR.

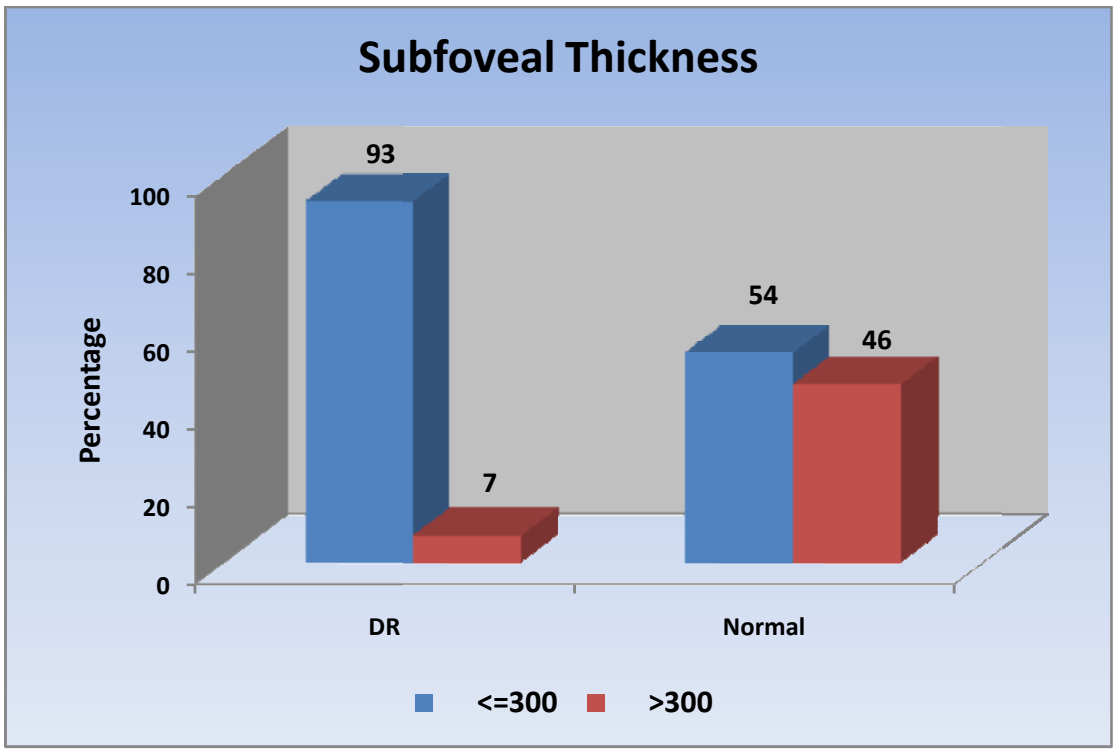


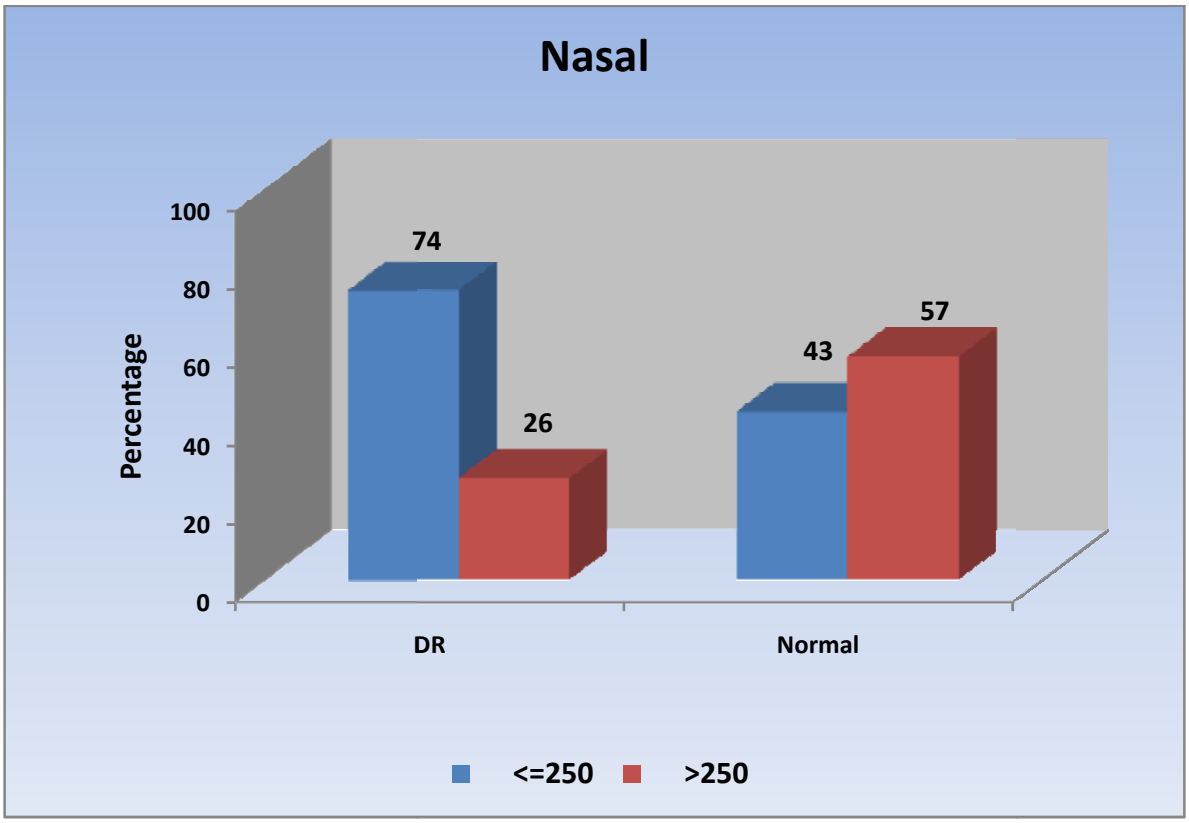
CHOROIDAL THICKNESS

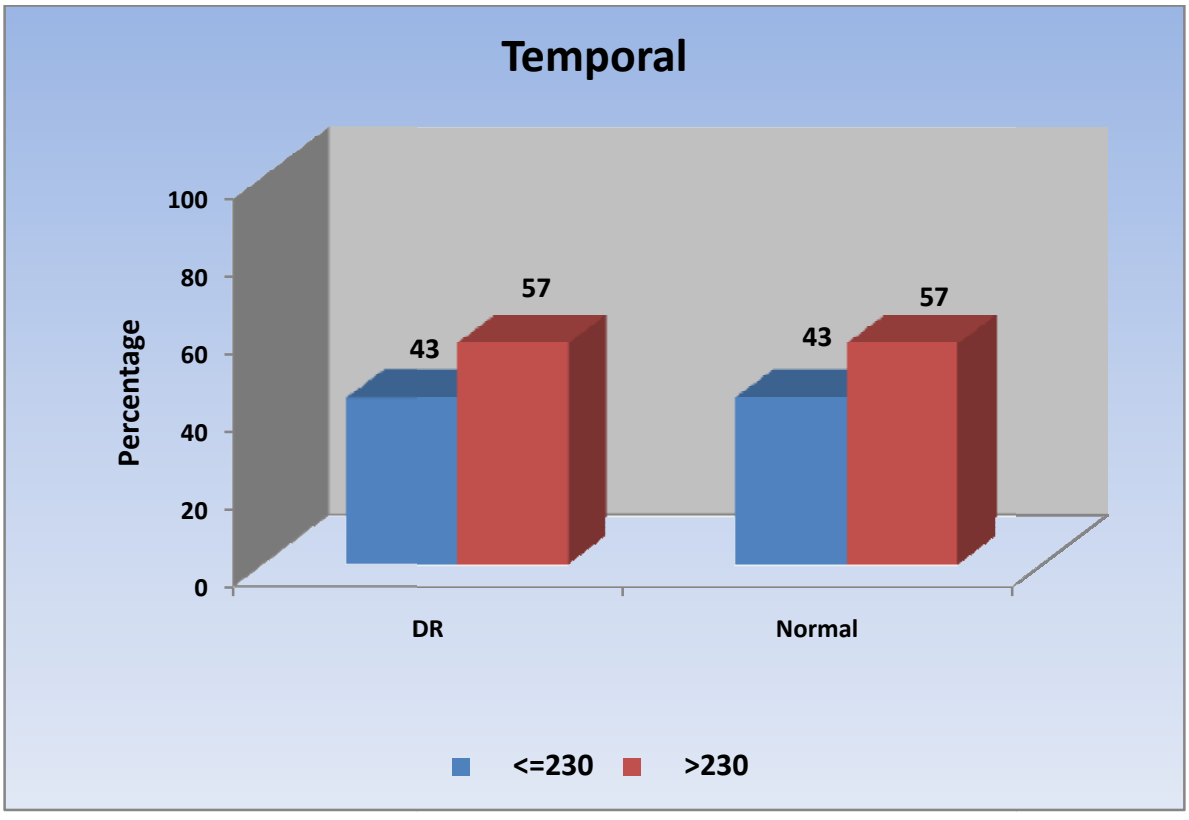
Choroidal Thickness	Group		Total (n=88 eyes)	P - value
	Normal (n=46 eyes)	*Diabetic Retinopathy (n=42 eyes)*		
Sub foveal				
Mean(SD)	311.32(68.2)	260.00(33.9)	286.82(60.1)	<0.001
Min - Max	207 - 476.5	198 - 344	198 - 176.5	
Nasal				
Mean(SD)	274.54(71.9)	232.31(31.7)	254.16(59.8)	0.0007
Min - Max	147 - 456.5	169 - 324	147 - 456.5	
Temporal				
Mean(SD)	258.26(70.7)	242.12(33.0)	250.47(56.1)	0.1729
Min - Max	147 - 432	162 - 337	147 - 432	

Mean sub foveal thickness was 260.00 in Diabetic Retinopathy group and 311.32 in Normal group, it was also statistically significant difference between group (P-value<0.001, using t-test). Mean Nasal thickness was 232.31 in Diabetic retinopathy group and 274.54 in normal group, it was also statistically significant different between groups (P-value=0.0007, using t-test). Mean temporal thickness was 242.12 in Diabetic retinopathy group and 258.26 in normal group, it was showing not statistically significant different between groups (P-value=0.173, using t-test). Category of choroidal thickness was shown in below table.

	Group		Total
	DR	Normal	
Subfoveal thickness			
<=300	39(92.9)	25(54.3)	64(72.7)
>300	3(7.1)	21(45.7)	24(27.3)
Nasal			
<=250	31(73.8)	20(43.5)	51(57.9)
>250	11(26.2)	26(56.5)	37(42.1)
Temporal			
<=230	18(42.9)	20(43.5)	38(43.2)
>230	24(57.1)	26(56.5)	50(56.8)



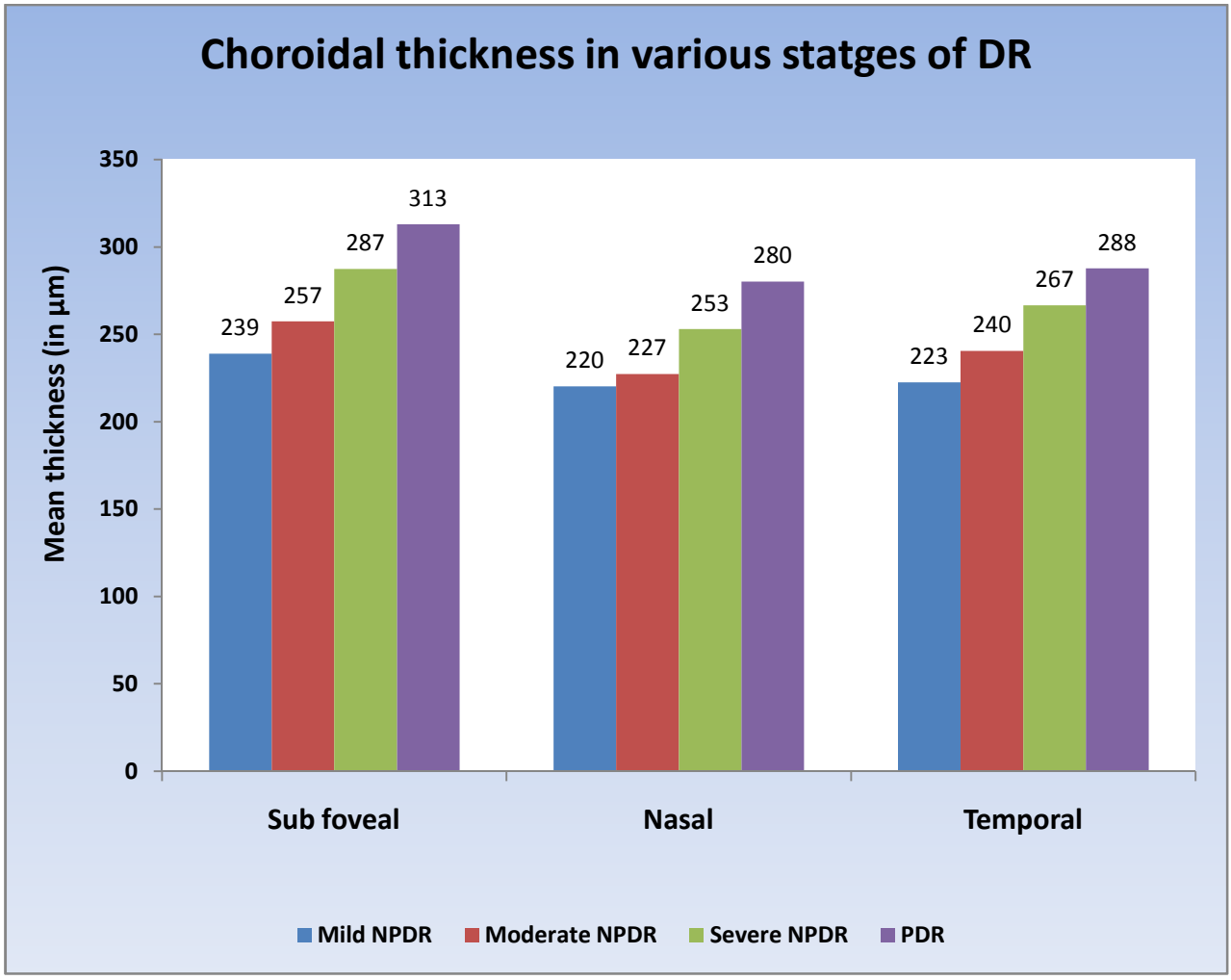

Nasal
Percentage
100
80
60
40
20
0
74
26
43
57
DR
Normal
<=250
>250


Temporal
Percentage
100
80
60
40
20
0
43
57
43
57
DR
Normal
<=230
>230

CHOROIDAL THICKNESS IN VARIOUS STAGES OF DR

Choroid Thickness	**DR stages [Mean(SD)]**				**Total (n=42 eyes)**
	Mild NPDR (n=11 eyes)	***Moderate NPDR (n=24 eyes)***	***Severe NPDR (n=3 eyes)***	***PDR (n=4 eyes)***	
Sub foveal Mean(SD) Min - Max	238.91(20.4) 200 - 272	257.42(31.3) 198 - 320	287.33(9.7) 279 - 298	313.00(23.1) 293 - 344	260.00(33.9) 198 - 344
Nasal Mean(SD) Min - Max	220.27(26.0) 169 - 265	227.25(26.0) 189 - 279	253.00(27.8) 228 - 283	280.25(40.0) 227 - 324	232.31(31.7) 169 - 324
Temporal Mean(SD) Min - Max	222.55(28.7) 162 - 275	240.42(26.7) 192 - 293	266.67(16.9) 255 - 286	287.75(41.2) 242 - 337	242.12(33.0) 162 - 337

Mean Subfoveal thickness was 238.91, 257.42, 287.33 and 313 in mild NPDR, moderate NPDR, Severe NPDR and PDR respectively. Mean Nasal thickness was 220.27, 227.25, 253.00 and 280.25 in mild NPDR, moderate NPDR, Severe NPDR and PDR respectively. Mean temporal thickness was 222.55, 240.42, 266.67 and 287.75 in mild NPDR, moderate NPDR, Severe NPDR and PDR respectively. All these three choroidal thicknesses was increase as severity of DR stage was increase.

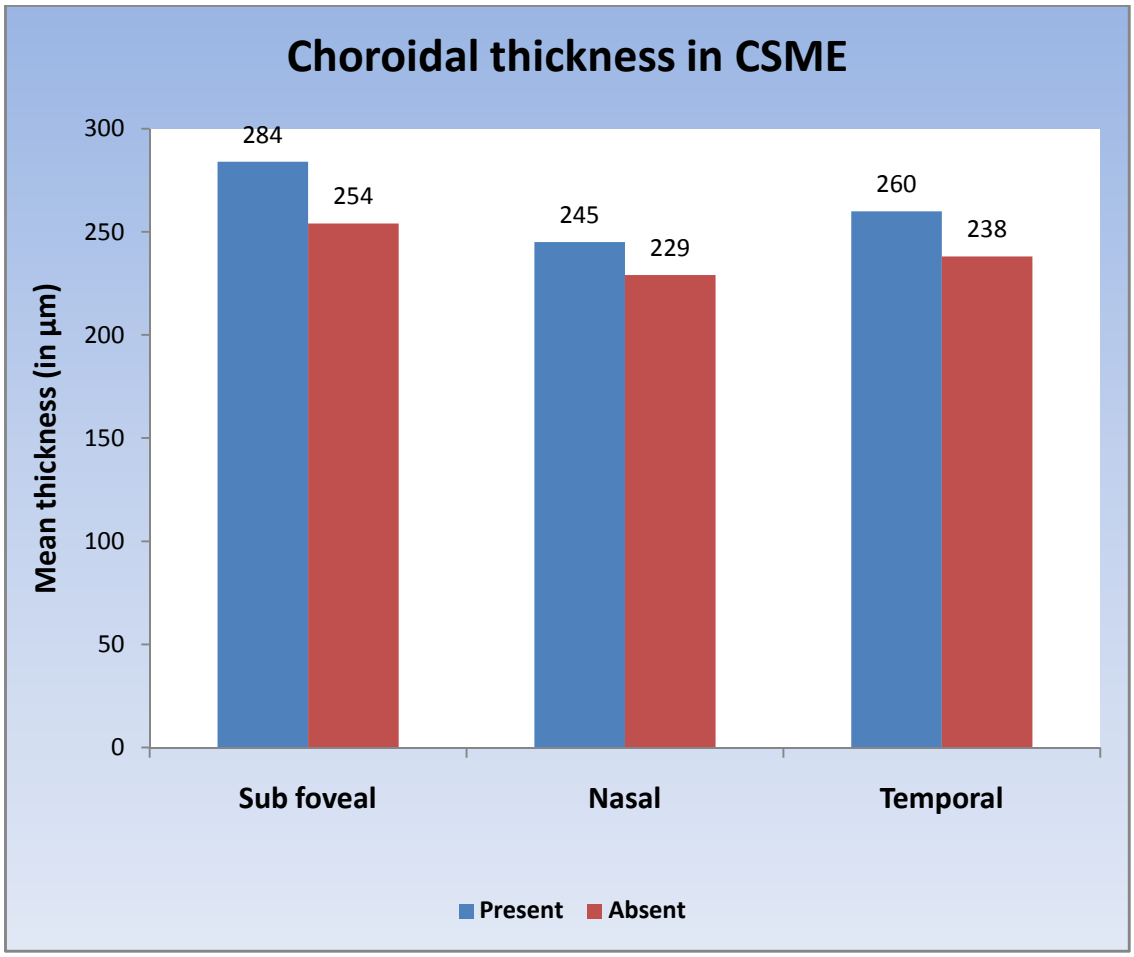

Choroidal thickness in various statges of DR
Mean thickness (in µm)
350
300
250
200
150
100
50
0
239
257
287
313
220
227
253
280
223
240
267
288
Sub foveal
Nasal
Temporal
Mild NPDR
Moderate NPDR
Severe NPDR
PDR

CHOROIDAL THICKNESS IN CSME

Choroid Thickness	**CSME [Mean(SD)]**		**P - value**
	Present (n=8 eyes)	*Absent (n=34 eyes)*	
Sub foveal			
Mean(SD)	284.38(19.8)	254.26(34.1)	0.022
Min - Max	257-320	198-344	
Nasal			
Mean(SD)	245.38(24.2)	229.24(32.8)	0.199
Min - Max	215-283	169-324	
Temporal			
Mean(SD)	259.88(19.5)	237.94(34.4)	0.091
Min - Max	229-286	162-337	

Mean subfoveal thickness was 284.38 in CSME and 254.26 in Non-CSME. It was showing statistical difference between CSME and Non-CSME group (P-value=0.022, using t-test). Mean Nasal thickness was 245.38 and 229.24 in CSME and Non-CSME group, there was no statistical difference (P-value=0.199, using t-test). Mean temporal thickness was 259.88 and 237.94 in CSME and non-CSME group respectively, it was not showing statistically significant difference (P-value = 0.091, using t-test).

Choroidal Thickness	CSME	NORMAL	P-value
Subfoveal µm Mean (SD) Min-Max	 284.38 257-320	 311.31 207 -476.5	 0.276



DISCUSSION

Choroid is an important vascular tissue which supplies the outer RPE and photoreceptors. The main functions of choroid are:

1. Thermoregulation,
2. Changes in choroidal thickness may change the position of the retina
3. Secretion of growth factors. (It play a role in emmetropization, ie: It helps in the adjustment of eye shapeduring growth to correct myopia or hypermetropia.)[18]

The choroid is the mainstay for blood supply to the retina. During nocturnal periods the photoreceptors consume more oxygen and that is supplied by the choroid (90 %) [18].The blood flow in the choroid is the highest of any tissue in the body. The high transport of oxygen from the choroid, despite the barriers of Bruch's membrane and the retinal pigment epithelium is because of this high blood flow.[18]

In humans, at birth the choroid is approximately 200 μm thick and by 90 years of age it decreases to around 80 μm[51]. Spaideet al[4] in his study found that the choroidal thickness decreases with age. Studies have also proven that certain conditions affect the choroidal thickness.

In diabetes, Studies have shown that the choroid is also involved and that diabetic choroidopathy can be used as a predictor for the occurrence of Diabetic retinopathy. [2,53]

Weinberger et al[2] showed that by FFA that both hyper and hypoflourescent spots were present in diabetic patients at the choroidal level. Pathologic findings included increased blood vessel tortuosity, focal vascular dilatation and narrowing, hypercellularity, vascular loops and formation of microaneurysm, nonperfused areas.There was also formation of sinus-like structure between the choroidal lobules. In the same study using ICG they described a salt and pepper appearance of the choroid which indicated delayed filling of the choriocapillaris, suggesting that there was presence of ischemia. It further proved the presence of diabetic choroidopathy which could be an predictor of retinal involvement. Zaharia et al[52] in his study noted that there is delayed choroidal lobular filling in diabetic patients even before clinical appearance of DR suggesting that there choroidal involvement before the retina in involved.

Nagoka et al[27] in his study on choroidal blood flow in the foveal region of diabetic patients found that the flow is decreased in early NPDR stages and was very much decreased in patients with diabetic macular edema. He also stated that the changes occurring in the choriocapillaris may occur well before the onset of diabetic retinopathy.

Hidayat et al[3] in his study noted that there was significant narrowing of the choriocapillaris in type 1 diabetic patients. Choroidal compromise was attributed to

1. Capillary drop-out with or without fibrosis
2. Basement membrane accumulation causing significant luminal narrowing of the choriocapillaris.
3. Endothelial hypertrophy in eyes with severely advanced disease.

Savage et al[54] on his study on pulsatile blood flow in various stages of DR showed that the Pulsatile ocular blood flow increased from mild to severe NPDR. The choroidal blood flow was found to be elevated in these groups but decreased in PRP treated eyes. Studies also found that the rise in choroidal blood flow mirrors the increase in renal blood flow[55-56] in moderate to severe NPDR.

Chhablani et al[56] in his study on normal Indian population found that the choroid was thickest subfoveally and thinnest nasally. He also found that CT had an negative correlation with age.

Unsal et al[42] in his study which was a Retrospective cross sectional research where 151 eyes from 8o patients with DR and 40 eyes of 20 healthy individuals. The DR patients were grouped into NPDR, Mild – moderate NPDR with Macular edema and proliferative diabetic retinopathy.

Choroidal thickness was measured using an optovueRTVue 100-2. They came to a conclusion that Choroidal thickness was found to be significantly decreased in DME (206.8 micrometers) and PDR (203.8 micrometers) groups when compared with normal group (259 micrometers).

Kim et al[1] in his study on 235 eyes from 145 patients ,195 eyes which had no ocular treatment and 40 eyes with prior history of PRP done for PDR were divided into no DR, Mild/Moderate nonproliferative DR (NPDR) ,severe NPDR ,PDR and PRP treated eyes.

The choroidal thickness was measured using the Heidelberg spectralis OCT. They came to a conclusion that the choroid was significantly thicker in DME than other DR groups and that the severity increased as it progressed from Mild NPDR to PDR and the choroid was thinner in PRP treated eyes.

Regatieri et al[35] in his study on 49 eyes of 49 Diabetic retinopathy patients and 24 aged matched normal subjects where the patients were split into 3 groups: Mild –moderate DR with no DME, Mild –Moderate DR with DME and treated Proliferative DR without DME.The choroidal thickness was measured using Cirrus HD OCT.

They concluded that choroidal thickness is altered in relation to the severity of retinopathy. Choroidal thickness is significantly reduced in the presence of DME.

Adhi et al[34] in his study where 33 eyes of patients with DR and 24 eyes of 24 controls were included in his study. Patients were split into 3 groups : NPDR with DME, PDR with DME and DME alone.

Spectral domain OCT (cirrus-HD) was used for measuring the choroidal thickness. They concluded that Sub foveal choroidal thickness, subfoveal medium choroidal vessel layer and choriocapillaries thickness is reduced markedly in Proliferative DR , Diabetic Macular oedema.

In our study we found that the subfoveal choroid was thinner in the DR group than the control group ($P<0.001$) . We found that the thickness increased as the severity of the disease progressed as the severity progressed..The choroidal thickness was thinner in DR patients (**260.00 micrometres)** than the control group (311.32micrometres).Among the DR patients the choroid was thicker in the PDR group (313 micrometres) and the DME groups (283 micrometres) . We also found that the choroid was thickest under the fovea and thinnest nasally than temporally .But in our study we had just taken one measurement at 500 micrometres. nasally and temporally.

The mean subfoveal thickness is 238.91,257.42,287.33 and 313 µm in mild NPDR, moderate, severe NPDR and PDR respectively. This is significantly less than the thickness in the controls where the mean thickness was 311.32 µm.Similar results were shown in a study,where the SFCT was shown to be less than the controls.[57]Chabblani et al[56] in his study has shown that choroidal thickness has been shown to be significantly related to age with an approximate decrease in CT of 1.18µm every year.Spaide et al[57] in

his study showed that there is a decrease in choroidal thickness by 15.6 micrometres with each decade of life.In our studythe mean age of the control group was 47 years and the DR group was 56.05years, thus the control group was 9 years younger than the diabetics and hence the lesser choroidal thickness in the study cohort.

Our study data shows that there has been a consistent increase in choroidal thickness with the increase in severity of DR which corroborates with the study findings of Kim et al[1].In his study, heattributed the thickness of these findings to an increased production of VEGF or other cytokines causing choroidal vasodilation as well as elevation in choroidal blood flow. These changes subsequently increased the thickness of the choroidal vascular layer, especially in patients with severe NPDR or PDR.Savage et al[53] noted in his study that there was an increase in the choroidal blood flow as the severity of DR progressed thus contributing to the increase in thickness.

The subfoveal choroidal thickness was more in the CSME group (284.38µm) as compared to the non CSME group (254.26µm) which is in accordance with the findings by Kim et al[1],where thickness was more in the DME group as compared with the no DME groups.

In this study we did not find any statistically significant difference between the subfoveal choroidal thickness in the CSME (284.38 μm**)** with diabetic retinopathy group and the controls (311 μm), which shows that in patients of CSME the CT increases which corroborates with other studies [1,57].

But the findings of the present study have to be corroborated with a bigger sample size and age matched subjects in both arms.

LIMITATIONS

1. Small sample size,particularly in the severe NPDR, CSME and PDR group.
2. There was significant difference in the age of the normal and DR groups that may have an effect on the outcome of the finding that diabetic choroid is thinner.
3. Hba1c was not used as an investigation to know the diabetic control of the patients enrolled in the study.
4. Diabetic patients with no DR were not included in this study.

CONCLUSION

In conclusion this study shows EDI OCT has an important role in the assessment of choroid in various stages of DR. This study also shows that the choroidal thickness increases as the severity of DR increases.

Further studies with a larger sample are necessary in wake of the findings of the present study so as to analyse the cause and effect relationship between DR grade and choroidal thickness by EDI OCT.

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Choroid Thickness in Various Stages of DR

Proforma for Thesis Study

Name:

MR NO: Study No:

Age: Sex :

Diabetic details:Other systemic illness:

Duration of diabetes: HTN ☐

HBA1c: Lipid Profile ☐

Details of Treatment: Renal ☐

Ocular History:

Any Surgery : Yes ☐ No ☐

If yes when: Nature of Surgery:

Any Intravitreal Injections/LASER: Yes ☐ NO ☐, If yes when: ☐

Using Ocular Medications: Yes ☐

Ocular Examination:

BCVA: RE - LE-

Anterior segment:

Normal ☐

Abnormal ☐ If yes mention condition :

Posterior segment:

Normal ☐ DR ☐

DR:

RE ☐ LE ☐

Grade of DR [RE]:

Mild / Moderate ☐ Severe ☐ PDR ☐

CSME : Present ☐ Absent ☐

Grade of DR [LE]:

Mild / Moderate ☐ Severe ☐ PDR ☐

CSME : Present ☐ Absent ☐

Fundus Photography: **RE** ☐ **LE** ☐

Choroidal thickness:

Area	RE	LE
Sub foveal		
Nasal		
Temporal		

ABBREVIATIONS

DR	–	Diabetic retinopathy
CT	–	Choroidal thickness
NPDR	–	Non proliferative Diabetic retinopathy
PDR	–	Proliferative diabetic retinopathy
CSME	–	Clinically significant macular oedema
DME	–	Diabetic macular oedema
Ch BF	–	Choroidal blood flow
EDI –OCT	–	Enhanced depth imaging optical coherence tomography
RPE	–	Retinal pigment epithelium

MASTER CHART - DIABETIC RETINOPATHY

S.NO	MR NO	Name	Age	Sex	RBS	Duration of diabetes	Treatment diab	HTN	Cholesterol	Renal	Ocular surgery	Duration_ocular surgery	BCVA RE	BCVA LE	AS RE	AS LE	DR RE	DR LE	Grade RE	Grade LE	CSME RE	CSME LE	Subfoveal RE	Subfoveal LE	Nasal RE	Nasal LE	Temporal RE	Temporal LE
1	4037762	sulochana	58	f	211	5yrs	On oral tab	Nil	Nil	Nil	Nil	Nil	6/6	6/6	Normal	normal	Present	Present	Mod	Mod	Nil	Nil	299	289	251	279	293	269
2	4041175	joy oonnommy	54	M	345	8 yrs	On oral tab	nil	nil	nil	nil	nil	4/60	6/18	Noral	normal	present	presnet	PDR	severe	nil	present	293	279	227	248	242	286
3	4026899	HakkimE	58	M	170	12yrs	oral tab	nil	nil	nil	nil	nil	6/6	6/6	Normal	normal	Present	Present	Mild	Mild	nil	nil	231	255	213	244	221	227
4	4028487	Muruganantham	57	M	337	5yrs	on oral tab	nil	nil	nil	nil	nil	6/6p	6/6p	Normal	Normal	Predent	Present	Mod	Mod	nil	nil	265	263	228	220	238	240
5	2866291	Chandra	50	F	115	10yrs	on oral tab	nil	nil	nil	nil	nil	6/12	6/9	Nuclear cat 2	Nuclear catract 1	present	present	mild	mild	nil	nil	200	234	196	169	196	162
6	3800971	Arumugam Ravindran	49	M	350	13yrs	oral tab	nil	nil	nil	nil	nil	6/9	6/6	Normal	normal	Present	present	Mild	Mild	nil	nil	265	272	204	241	210	231
7	4037325	chandrasekaran	58	M	123	15 days	oral tab	nil	nil	nil	nil	nil	6/12	6/9	Normal	normal	Present	Presevt	Mod	severe	nil	present	234	272	189	241	214	244
8	4062489	Sebastien	53	M	193	8ys	Insulin	nil	nil	nil	nil	nil	6/12	6/18	Normal	Normal	Present	Present	Mod	Mod	nil	nil	232	240	215	211	227	224
9	4010367	Sekaran	65	M	101	10yrs	oral tab	nil	nil	nil	nil	nil	6/18	6/12	Nuclear catract	Nuclear catarct1	Present	present	Mod	mod	present	present	320	295	265	249	280	270
10	4050786	gopal	49	M	168	10 months	oral tab	nil	nil	nil	nil	nil	6/18	6/12	Lens changes	Lens changes	Present	present	Mod	Mod	nil	nil	279	280	265	265	255	270
11	4035342	Seran	59	M	144	4 yrs	oral tab	nil	nil	nil	nil	nil	6/12	6/12	Nuclear catract 1	Nuclear cataract 2	Present	Present	Mod	Mod	nil	nil	248	232	217	207	240	235
12	3791297	Karuppaiah	52	M	135	3yrs	oral tab	nil	nil	nil	nil	nil	6/24	6/9	Lens changes	Lens changes	present	present	Sevre	Mod	present	nil	285	279	228	212	255	260
13	1692478	chenniappan	60	M	120	2ys	oral tab	nil	nil	nil	nil	nil	6/9	6/6	Lens changes	Lens changes	present	present	mild	mod	nil	nil	238	246	221	230	228	229
14	4112132	parameswari	52	F	148	5 months	oral tab	nil	nil	nil	nil	nil	6/12	6/9	Lens changes	Lens changes	present	present	mod	mod	nil	nil	251	286	231	231	227	258
15	4112730	mareeswaran	58	M	132	6yrs	oral tab	nil	nil	nil	nil	nil	6/36	6/12	nuc catract 2	nuc catract 1	present	present	mod	PDR	presnt	nil	273	317	259	287	262	303
16	411345	liyakath Ali	50	M	375	7yrs	oral tab	nil	nil	nil	nil	nil	6/60	6/60	Lens changes	Lens changes	present	present	PDR	PDR	nil	nil	344	298	324	283	324	269
17	4114386	Posa Ragurammaiah	62	M	146	2yrs	oral tab	nil	nil	nil	nil	nil	6/12	6/6	Lens changes	Lens changes	present	present	mild	mild	nil	nil	235	248	204	234	210	245
18	3099245	Mohan	55	M	216	10yrs	oral tab	nil	nil	nil	nil	nil	6/18	6/6	nuclear cat 1	nuc catract 1	present	present	mod	mild	nil	nil	248	220	234	204	245	203
19	3022755	Krishnakumari	62	F	230	12yrs	oral tab	nil	nil	nil	nil	nil	6/9	6/36	Lens changes	Lens changes	present	present	mod	mod	present	present	268	257	216	215	238	229
20	3037553	selvi	55	F	186	13 yrs	oral tab	nil	nil	nil	nil	nil	6/6	6/6	clear	clear	present	present	Mild	mod	nil	nil	230	218	216	218	230	229
21	2815439	Ahmed	61	M	187	10yrs	oral tab	nil	nil	nil	nil	nil	6/9	6/9	lenschanges	Lens changes	present	present	mod	mod	nil	nil	200	198	189	191	192	194

MASTER CHART - NORMAL DATA

S.NO	MR NO	Name	Age	Sex	Subfoveal RE	Subfoveal LE	Nasal RE	Nasal LE	Temporal RE	Temporal LE
1	1976238	PREMALATHA	50	F	280		249		258	
2	840830	GANESAN	45	M	406.5	383	378.5	341	225	288
3	1976231	DHANBAK	53	F	336.5	274	265.5	237.5	282	227
4	1683059	PALANISAMY	47	M	243.5	237.5	232	164	218.5	229
5	1977982	rengaraj	44	M	287.5		233		188	
6	1977917	SHABEER ALI	34	M	431.5	422.5	375.5	397	380.5	194.5
7	1977943	CHANDRASEKAR	44	M	377	292	317.5	292.5	344	269.5
8	1977927	RAJAGOPALAN	61	M	249	242	173	193	147.5	176.5
9	1977919	SARASWATHI	52	F	338	229	282	404	262	221.5
10	1978719	CHANDRASEKAR S	43	M	237.5	274	147	206	218.5	208.5
11	1436019	LOGAMBAL	41	F	333	459.5	328	396.5	383	397.5
12	1980374	S BABY	40	F	270.5	290	237.5	228	333	246
13	1980340	KANAMMAL	48	F	326.5	259.5	306	275.5	240	194.5
14	1980342	SHANMUGAM	67	M	293.5	271.5	287	247.5	272	176.5
15	1980359	CHINNAPONNU	45	F	276.5	280	178	272	179	199.5
16	1981179	chandrika	60	F	281.5	236	300	280	291.5	224
17	1981192	AMUTHA	48	F	354	349.5	315	299.5	272.5	302.5
18	1981219	REJINI	40	F	396.5	421.5	298.5	343	267	343.5
19	1981520	SRINIVASAN	50	M		302.5	236.5		252.5	
20	1984402	NALINI	52	F	352	282	275.5	229	348	285
21	1759415	S K SUDHA	33	F	359	330.5	317	346.5	346.5	297
22	1981594	BALAKRISHNAN	42	M	239.5	230.5	168	208	216	174
23	1984391	SAIDALI	59	M	324.5	219	231.5	214	233.5	147
24	1984424	NALLASAMY	40	M	207		196		157.5	
25	1984413	NIRMALADEVI	43	F	357	476.5	232.5	456.5	324.5	432

ARAVIND MEDICAL RESEARCH FOUNDATION
Institutional Ethics Committee
(Registration No.ECR/182/Inst/TN/2013 dated 20.04.2013)

12th February 2015

To

Dr.R.Ram Sudarshan
MS Resident
Aravind Eye Hospital
Madurai

Dear Dr.Ram Sudarshan,

Thesis Title: Study of Subfoveal choroidal thickness in various stages of Diabetic retinopathy using EDI OCT

IRB Code: IRB201500209

Thank you for submitting your thesis and seeking the approval from the ethics committee. The documents provided by you for consideration which include the thesis protocol and informed consent forms were reviewed for the research methodology and scientific content. The Ethical committee did not find any correction and has recommended the thesis to go ahead in the present form.

Thanking you

Yours Sincerely,

L Lalitha.

Dr.Lalitha Prajna
Member Secretary
Institutional Ethics Committee

MEMBER SECRETARY
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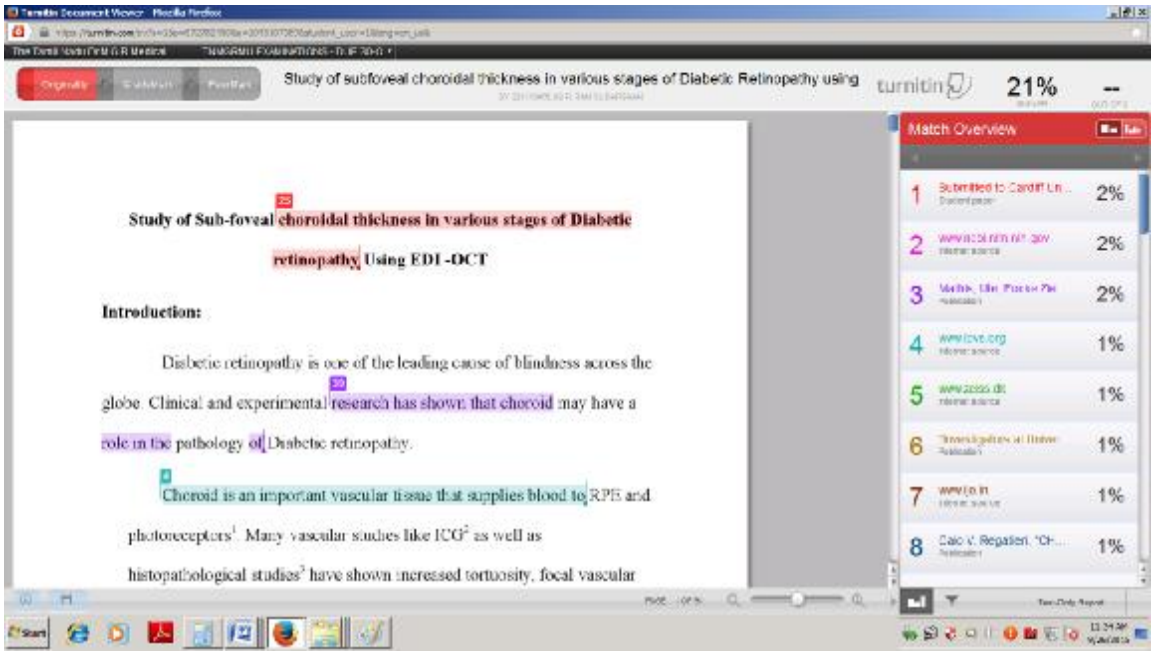
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Introduction:
Diabetic retinopathy is one of the leading cause of blindness across the globe. Clinical and experimental research has shown that choroid may have a role in the pathology of Diabetic retinopathy.
Choroid is an important vascular tissue that supplies blood to RPE and photoreceptors[1]. Many vascular studies like ICG[2] as well as histopathological studies[3] have shown increased tortuosity, focal vascular

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Introduction